Cognitive impairment in cocaine users: evidence from cross-sectional and longitudinal analyses

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Contents

Abstract

The United Nations Office on Drugs and Crime currently estimates the annual number of cocaine users at about 17 million people worldwide, resulting in a total retail market of about 85 billion USD per year (2011; 2013). Although the use of cocaine is a widespread public health issue, there are still many open questions considering its concrete consequences.

For now more than two decades, research has tried to examine the impact of cocaine use on cognition, primarily by focusing on dependent cocaine users. In recent years, the focus expanded to the more relevant type of recreational and non-dependent cocaine user (European Monitoring Center for Drugs and Drug Addiction, 2012). In this context, a growing body of literature consistently linked the long-term use of cocaine to different effects in cognition (Jovanovsky et al., 2005; Perry & Carroll, 2008), in particular to a persisting pattern of cognitive impairments and enhanced impulsivity. However, there is so far no clarification on the exact relation between the use of cocaine and cognitive functioning. Aetiology, causality, reversibility, and the extent of this association are still a matter of ongoing debate.

The present doctoral thesis aims to contribute to this research gap and seeks to clarify the long-term relation between the use of cocaine on the one hand and cognitive functioning and impulsivity on the other hand. The clarification of this issue is important not only with regard to general functioning in daily life, but also with regard to risk markers, prevention, treatment, and after-treatment strategies.

In the first paper (chapter 2), we examined whether cognitive performance is impaired in relatively pure recreational and dependent cocaine users. By means of a cross-sectional study, we compared the cognitive performance of 68 recreational and 30 dependent cocaine users with the performance of 68 stimulant-naïve controls. Whereas dependent cocaine users displayed broad cognitive impairments in the domains attention, working memory, declarative memory, and executive functions, recreational cocaine users performed in all four domains intermediate between controls and dependent users. Hence, cognitive deficits occur already at a recreational and non-dependent level of cocaine use. Moreover, correlation analyses revealed negative associations between the cognitive performance and long-term cocaine use parameters (cumulative dose, duration of use, hair metabolites) initially suggesting that cognitive impairments might be partially cocaine-induced. Accordingly, the risk for cognitive impairment was linked to ascending cumulative cocaine doses, in particular if estimated lifetime doses of 500g to 1000g cocaine were exceeded. Finally, an attention deficit hyperactivity disorder, craving, and age of onset proved to be important modulators of cognitive functioning in cocaine users.

In the second paper (chapter 3), we used the same cross-sectional sample to examine trait and motor impulsivity in recreational and dependent cocaine users. Our goal was to clarify the role of impulse control in cocaine addiction and non-dependent cocaine use. Compared with controls, recreational as well as dependent cocaine users exhibited higher trait impulsivity and novelty seeking scores.

Moreover, trait impulsivity scores correlated significantly with long-term cocaine intake parameters (cumulative dose, duration of use) and were strongly associated with symptoms of depression and attention deficit hyperactivity disorder. These findings suggest that increased trait impulsivity is not a specific feature of dependent cocaine use. By contrast, we found no associations between behavioral motor impulsivity measures and cocaine use parameters. However, it remains unclear if there is indeed a dissociation between trait and motor impulsivity or whether the differences rather highlight difficulties in the operationalization and measurement of motor impulsivity.

In the third paper (chapter 4), we intended to determine the relation between the pattern of cocaine use and the characteristics of cognitive functioning by means of a one-year longitudinal study including 57 cocaine users and 48 stimulant-naïve controls. Cognitive functioning was assessed by the same cognitive measures and domains as in the first paper. Our results suggest that substantially increased cocaine use within 1 year led to a deteriorated cognitive performance, primarily in the working memory. By contrast, decreased cocaine use generally improved cognition and showed the strongest enhancement in working and declarative memory, whereas users who completely ceased using cocaine seemed to recover entirely and attained a similar cognitive level as the control group. These results suggest that cognitive deficits are at least partially cocaine-induced but also reversible within one year. Seemingly, these cognitive changes in cocaine users are based on modifiable neuroplastic adaptations. However, these findings imply that abstinence is the best way to enhance cognitive performance in stimulant users in the long-run.

Overall, these results indicate at strong relation between the repeated use of cocaine and specific characteristics of cognitive functioning. First, recreational and dependent cocaine users displayed cognitive impairment. Second, there is an evident relation between the long-term use of cocaine and cognitive functioning. Third, both, recreational and dependent cocaine users displayed enhanced trait impulsivity and novelty seeking. Fourth, there is a close relationship between the changing pattern of cocaine use and the development of cognitive functioning.

Zusammenfassung

Nach einem Report des United Nations Office on Drugs and Crime (2013) konsumieren jährlich weltweit rund 17 Millionen Menschen Kokain. Der kumulierte Weltmarkt der Droge beläuft sich Schätzungen zufolge auf rund 85 Milliarden USD pro Jahr (United Nations Office on Drugs and Crime, 2011; 2013). Obwohl der Konsum von Kokain im Gesundheitswesen seit geraumer Zeit ein salientes Thema ist, sind die langfristigen Folgen nach wie vor nicht abschliessend geklärt.

Die Forschung untersucht die langfristigen Effekte des Kokainkonsums auf die Kognition seit ungefähr zwei Jahrzehnten. Der Fokus richtete sich dabei lange Zeit fast ausschliesslich auf die abhängigen Konsumenten. Erst in den letzten Jahren rückte zunehmend auch der weit häufiger auftretende Typus des gelegentlichen Kokainkonsumenten (European Monitoring Center for Drugs and Drug Addiction, 2012) ins Blickfeld der Wissenschaft. Im Rahmen dieser Forschung zeigte sich mit der Zeit ein konsistenter Zusammenhang zwischen dem langfristigen Konsum von Kokain und Effekten in verschiedenen Funktionen der kognitiven Kontrolle – insbesondere anhaltende Einbussen der kognitiven Leistungsfähigkeit und eine erhöhte Impulsivität (Jovanovsky et al., 2005; Perry & Carroll, 2008). Eine eindeutige Klärung der Zusammenhänge gibt es bis dato aber nicht, so sind speziell die relevanten Aspekte Ätiologie, Kausalität, Quantität und Reversibilität noch nicht abschliessend geklärt.

Basierend auf diesen Erkenntnissen soll es deshalb im Rahmen dieser Arbeit darum gehen, die langfristige Beziehung zwischen dem Kokainkonsum einerseits sowie der kognitiven Leistungsfähigkeit und Impulsivität andererseits zu untersuchen. Die Klärung dieser Zusammenhänge ist nicht nur in Bezug auf die Folgen für das tägliche Leben, sondern speziell auch im Hinblick auf Risikofaktoren, Prävention, Therapie und deren Folge-Begleitung von grosser Relevanz.

In einer ersten Studie (Kapitel 2) wurden in einem Querschnittdesign anhand einer umfangreichen neuropsychologischen Testbatterie die kognitiven Leistungen gelegentlicher (n=68) und abhängiger Kokainkonsumenten (n=30) mit denen einer Kokain-unerfahrenen Kontrollgruppe (n=68) verglichen. Dabei zeigten abhängige Kokainkonsumenten starke Einbussen in der Aufmerksamkeit, dem Arbeitsgedächntis, dem deklarativen Gedächtnis sowie den exekutiven Funktionen. Gelegentliche Kokainkonsumenten offenbarten ebenfalls relevante, allerdings etwas schwächere Einbussen und lagen in allen vier Bereichen zwischen den abhängigen Konsumenten und den Kontrollen. Negative Korrelationen zwischen der kognitiven Leistungsfähigkeit und langfristigen Parametern des Kokainkonsums (kumulierte Gesamtmenge, Dauer des Konsums, Kokain-Metaboliten in den Haaren) deuteten überdies an, dass diese Einbussen Kokain-induziert sein könnten. Zudem zeigte sich, dass das Risiko kognitiver Einbussen mit steigendem Kokainkonsum zunimmt, wobei dies insbesondere ab einer kumulierten Gesamtmenge von 500g bis 1000g der Fall ist. Weitere Analysen konnten ausserdem aufzeigen, dass eine Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung, das starke Verlangen

nach Kokain (craving) sowie das Alter bei Konsumbeginn wichtige moderierende Faktoren für das kognitive Funktionieren bei Kokainkonsumenten sind.

In der zweiten Studie (Kapitel 3) wurde dieselbe Probandenstichprobe im Hinblick auf verschiedene Aspekte der Impulsivität untersucht. Das zentrale Thema war dabei das Wesen der Impulskontrolle bei gelegentlichen und abhängigen Kokainkonsumenten. Die Resultate zeigten sowohl bei gelegentlichen als auch bei abhängigen Kokainkonsumenten eine deutlich erhöhte Trait-Impulsivität und ein höheres Neugierverhalten als bei den Kontrollen. Die Trait-Impulsivität korrelierte dabei mit langfristigen Parametern des Kokainkonsums (kumulierte Gesamtmenge, Dauer des Konsums) und variierte mit der Depressivitätsneigung sowie dem Ausmass der Aufmerksamkeitsdefizit-/Hyperaktivitätsstörung. Insgesamt zeigten diese Ergebnisse, dass eine erhöhte Trait-Impulsivität keine spezifische Eigenschaft der Drogenabhängigkeit ist, sondern bereits bei gelegentlichem Kokainkonsum auftritt. Im Gegensatz dazu fand sich kein Zusammenhang zwischen dem Kokainkonsum und der motorischen Impulsivität. Im Rahmen der vorhandenen Daten konnte aber nicht abschliessend geklärt werden, ob die unterschiedlichen Resultate zu Trait- und motorischer Impulsivität tatsächlich eine Dissoziation verschiedener Facetten der Impulsivität darstellen oder ob die Unterschiede vielmehr auf die Schwierigkeiten bei der Messung der motorischen Impulsivität zurückzuführen sind.

In der dritten Studie (Kapitel 4) wurde der Zusammenhang zwischen der Veränderung des Kokainkonsums und Charakteristiken der kognitiven Leistungsfähigkeit untersucht. Im Rahmen einer einjährigen Längsschnittstudie mit 48 Kokain-unerfahrenen Probanden und 57 Kokainkonsumenten zeigte sich, dass Kokainkonsumenten, die ihren Konsum innerhalb eines Jahres merklich steigerten, weitere kognitive Einbussen – insbesondere im Arbeitsgedächtnis – zu verzeichnen hatten. Kokainkonsumenten, die ihren Konsum innerhalb eines Jahres substanziell verringerten, zeigten (besonders im Arbeitsgedächtnis und deklarativen Gedächtnis) eine Verbesserung der kognitiven Leistungsfähigkeit, wobei die komplett abstinenten Konsumenten sogar wieder das kognitive Niveau der Kontrollgruppe erreichten. Insgesamt weisen diese Resultate auf Kokain-induzierte kognitive Defizite hin, die zumindest teilweise auch reversibel zu sein scheinen. Die Befunde zur Reversibilität dieser Effekte deuten an, dass es sich dabei eher um neuroplastische und adaptive Prozesse handelt, die vermutlich auch psychotherapeutisch oder pharmakologisch modulierbar sind. Die Daten legen damit nahe, dass Abstinenz der beste Weg ist, langfristig die kognitive Leistungsfähigkeit von Kokainkonsumenten zu steigern.

Zusammengefasst bestätigen die Resultate der drei Studien die vermutete enge Beziehung zwischen dem langfristigen Kokainkonsum und spezifischen Charakteristika der kognitiven Kontrolle: Erstens zeigten gelegentliche und abhängige Kokainkonsumenten kognitive Dysfunktionen. Zweitens korrelierten diese Einbussen mit langfristigen Parametern des Kokainkonsums. Drittens offenbarten nicht nur abhängige, sondern auch gelegentliche Kokainkonsumenten eine erhöhte Trait-Impulsivität. Viertens zeigte sich im Längsschnittdesign eine enge Beziehung zwischen dem Verlauf des Kokainkonsums und der Entwicklung der kognitiven Leistungsfähigkeit.

1 General Introduction

1.1 Thesis outline

The use of cocaine and its direct and indirect consequences are well discussed public health issues (Degenhardt, 2012). Since the beginning of the nineties, research has tried to examine the relation between the repeated use of cocaine and physical, psychological, and biological consequences. Thereby, cocaine use revealed to be strongly linked to different aspects of cognitive functioning, a general term comprising a broad palette of cognitive processes (Garavan and Hester, 2007; Jovanovski et al., 2005; Lesh et al., 2011). In this research, cocaine users displayed strong drug-associated deficits in different aspects of cognitive functioning (Jovanovski et al., 2005; Perry and Carroll, 2008). Although a substantial part of the cocaine users consumed the stimulant in a recreational and non-dependent manner (European Monitoring Centre for Drugs and Drug Addiction, 2012), most research has focused on the long-term consequences of chronic and dependent cocaine use. Accordingly, there is only limited knowledge regarding the consequences of recreational, increasing, decreasing, or ceasing cocaine use to date.

In sum, there is still no clarification on the relation between the extent of cocaine use and the development of different aspects of cognitive functioning. However, these issues are important for the personal, public, and official dealing with the drug. Therefore, the present doctoral thesis aims to contribute to bridging this research gap and investigates the long-term relation between the use of cocaine and some important aspects of cognitive functioning: cognitive control in terms of impulsivity and cognition in terms of attention, memory, and executive functions.

1.2 General facts about cocaine

Cocaine (benzoylmethylecgonine, $C_{17}H_{21}NO_4$) is a psychostimulant drug that is obtained from the leaves of the Erythroxylon coca plant, which primarily grows in the South American Andes (Egred and Davis, 2005; Karch, 2002). It can be ingested in different ways, but it is mostly snorted, injected, or smoked as freebase or crack. Onset (some seconds to 20 minutes), duration (some minutes up to approximately one hour) and impact of acute effects vary considerably and depend on the amount of cocaine taken and its route of administration. Cocaine increases the availability of the neurotransmitters dopamine, serotonin, and norepinephrine in the synaptic cleft via a blockade of the corresponding presynaptic monoamine transporters (Bolla and Cadet, 2007; Ritz et al., 1990). These effects lead to a feeling of euphoria (“high”), increased energy, rapid thinking, increased self-confidence, sensory alertness, loss of appetite, and reduced sleep requirement (Cosgrove and Staley, 2007; Jenkins, 2007; Mash, 2007). Because cocaine metabolizes fast, the stage of euphoria is generally followed by a “crash” period of deprivation symptoms that comprises decreased energy, dysphoria, cognitive dysfunction, and craving (Abadinsky, 2008; Mash, 2007). This sequence of positive feelings

followed by negative side effects often leads to the desire of additional cocaine use, frequently resulting in binge-taking behavior or repeated cocaine use (Martin-Soelch, 2010).

1.3 Epidemiology of cocaine use

The United Nations Office on Drugs and Crime (2011) estimates the annual total retail market for cocaine of up to 85 billion USD. With 13.9 million to 20.7 million cocaine users in 2011 (0.3%-0.5% of the global population aged 15 to 64), cocaine is one of the most used illicit drugs worldwide (United Nations Office on Drugs and Crime, 2013). Although the use of cocaine is generally stable at the global level, different regions feature different trends. In recent years (since 2006), North America has seen a marked decline, whereas Europe remained relatively stable, and Africa, Asia, Oceania, and South America showed a substantial increase (United Nations Office on Drugs and Crime, 2013). Today, North America and Europe with 4.6 million annual cocaine users each are estimated to account for approximately one half of the global cocaine users.

In Europe, the prevalence varies regionally. Whereas high levels of cocaine use are observed in some mostly western European countries, the use of cocaine remains limited elsewhere. Recent data from the European Monitoring Centre for Drugs and Drug Addiction (2012) even raise the possibility that the drug's popularity is not only stabilizing but partially declining.

In Switzerland, the Federal Office of Public Health (2012) estimated that people aged over 15 have a lifetime prevalence of 3%, while 0.4% are supposed to have used cocaine in the last 12 months. As per today, cocaine remains the second most commonly used illicit drug in Switzerland (Federal Office of Public Health, 2012) and Europe (European Monitoring Centre for Drugs and Drug Addiction, 2012).

Cocaine users exhibit a wide range of usage patterns, starting from one-time tempters to highly dependent users. Although cocaine is considered to be an addictive drug (Nutt et al., 2007), by far not everyone who tries cocaine becomes dependent. It has been estimated that about 5-6% of the cocaine users develop a dependency within the first year of use (Wagner and Anthony, 2002), whereas approximately 16% developed a cocaine dependency in the long run (Anthony, 2002; Wagner and Anthony, 2002). Therefore, focusing only on regular users (and excluding one-time tempters) leaves us with the simplistic dichotomy of recreational users, tending to use cocaine at special occasions, and dependent cocaine users (European Monitoring Centre for Drugs and Drug Addiction, 2012).

1.4 Cognitive functioning

Cognitive abilities are individual functional properties (Lezak et al., 2004) that encompass a broad class of mental operations including a wide range of cognitive domains and functions, generally located in the frontal and more specifically the prefrontal cortex (Badre, 2008; Cabeza and Nyberg, 2000; Garavan and Hester, 2007; Yucel and Lubman, 2007). Although brain areas and neural processes underlying drug addiction clearly overlap with those that support cognitive functions (Gould, 2010), the exact role of cognitive functioning with regard to substance use in general and cocaine use in particular is still an open question.

On the one hand, drug use is considered to be an affective or emotional phenomenon including psychological aspects such as reward, craving, or pressure (Garavan and Hester, 2007; Yucel and Lubman, 2007), on the other hand it is a volitional and in its own way even rational decision towards a certain behavior. Therefore, cognitive processes are crucially associated with the repeated use of cocaine and are furthermore important to understand the mechanisms of recreational and dependent cocaine use as well as cocaine abstinence and/or relapse processes (Garavan and Hester, 2007; Gould, 2010). In this sense, drug addiction is considered to be a disorder of altered cognition (Gould, 2010). However, a recent addiction model recommends to characterize addiction as a two-stage process (Gould, 2010). Whereas the first stage comprises the increasingly uncontrolled recreational use culminating in a transition to dependent use, the second stage of the addictive process includes clinical attributes and cognitive alterations (Gould, 2010). Because different cognitive functions seem to be relevant at any stage of the drug use cycle (Garavan and Hester, 2007), this raises the question about its constitution and characteristics – is impaired cognitive functioning a preexistent trait, a drug-induced consequence, or both? In the context of this doctoral thesis, we limit the focus on some important aspects of cognitive functioning, commonly considered to be relevant in association with the use of cocaine (Garavan and Hester, 2007; Jovanovski et al., 2005): cognitive control in terms of impulsivity and cognition in terms of attention, memory, and executive functions.

1.5 Cocaine use and cognitive functioning: Behavioral research

To date, multiple studies have demonstrated that dependent cocaine use is associated with broad deficits in cognitive functioning, including foremost attention, memory, executive functions, decision-making, and various aspects of impulsivity (Jovanovski et al., 2005; Perry and Carroll, 2008). In particular, studies focusing on sustained attention found more or less consistent results and drew the picture of solid deficits in chronic cocaine users (Abi-Saab et al., 2005; Cunha et al., 2004; Goldstein et al., 2004; Jovanovski et al., 2005; Pace-Schott et al., 2008; Woicik et al., 2009). Findings considering different memory components are less consistent but indicate likewise cocaine-related

visual and verbal memory impairments (Abi-Saab et al., 2005; Cunha et al., 2004; Goldstein et al., 2004; Jovanovski et al., 2005; Pace-Schott et al., 2008; Woicik et al., 2009). Furthermore, although studies focusing on the heterogeneous concept of executive functions yielded inconsistent findings (Jovanovski et al., 2005), there still is a tendency that cocaine users display impairments foremost in response inhibition, decision-making, and cognitive flexibility (Beveridge et al., 2008; Cunha et al., 2004; Woicik et al., 2009). Notably, the rare inconsistencies within these chronic user data are mainly based on theoretical and methodological barriers such as different concept specifications, test batteries, psychological comorbidities, or different patterns of cocaine or polydrug use (Beveridge et al., 2008; Rogers and Robbins, 2001). Moreover, although attention-deficit hyperactivity disorder was frequently associated with substance use disorders (Perez de Los Cobos et al., 2011; Wilson, 2007), its direct impact on cognition has not been systematically investigated so far.

With regard to impulsivity, it should be noted that different instruments measure a wide range of attitudes generally termed as “impulsive” (Dawe et al., 2004; de Wit, 2009). While impulsive action or choice in terms of inhibition and decision-making are generally considered to be part of the executive functions (Miyake et al., 2000) and measured with behavioral tasks (Winstanley et al., 2010), other facets such as trait impulsivity, novelty seeking, and delay discounting are mostly analyzed in separate studies and assessed by self-report questionnaires. However, cognitive control includes both, behavioral and trait impulsivity, and in both cases, chronic cocaine use has consistently been associated with higher impulsivity scores (Ersche et al., 2010; Perry and Carroll, 2008; Verdejo-Garcia et al., 2008). Similar to in studies on cognitive functioning, there is still no clarification considering the specific impact of the attention-deficit hyperactivity disorder on impulsivity in cocaine users.

While most studies focused on the dependent use of cocaine, relatively little is known about the substantial number of recreational or occasional but non-dependent cocaine users (European Monitoring Center for Drugs and Drug Addiction, 2011). Only in recent years research has started to systematically investigate cognitive effects of recreational cocaine use (Colzato et al., 2009b). An experiment with non-human primates suggested that repeated short-term exposure to cocaine is sufficient to produce selective deficits in cognitive functions dependent on the orbitofrontal cortex (Olausson et al., 2007). Preliminary data on neurocognitive functioning in recreational cocaine users draw a similar picture by indicating that already small and infrequent doses of cocaine affect different cognitive components. These studies include deficits in attention, visuo-spatial perception, verbal memory (Rahman and Clarke, 2005), fear recognition (Kemmis et al., 2007), inhibitory behavioral control (Colzato et al., 2007), the scope of visual attention (Colzato et al., 2009b), cognitive flexibility (Colzato et al., 2009a), inhibition of return (Colzato and Hommel, 2009), sustained attention, attentional shifting, spatial memory (Soar et al., 2012), and reduced spontaneous eyeblink rate, a supposed marker of striatal dopaminergic functioning (Colzato et al., 2008). Furthermore, recreational stimulant users with cocaine as the primary drug of use showed performance deficits in verbal

learning, recall, and recognition domains and displayed higher self-reported impulsivity (Reske et al., 2010b).

In sum, recent literature is characterized by the consensus that repeated cocaine use is associated with substantial cognitive impairments. However, some rare preliminary data from one to six months abstinent cocaine users in cross-sectional (Bolla et al., 1999; De Oliveira et al., 2009; van Holst and Schilt, 2011) and longitudinal studies (Bauer, 1996; Bolla et al., 2000; Di Sclafani et al., 2002; van Gorp et al., 1999) suggest cognitive recovering effects for abstinent cocaine users, particularly for those users with a longer abstinence duration (up to six months). Nonetheless, all of these studies focused exclusively on cocaine users who ceased their consumption and there is no published analysis investigating the cognitive development in decreasing or increasing cocaine users to date.

Altogether, these studies indicate cocaine-related post-acute deficits in cognitive functioning and impulsivity, while there is still no clarification on the exact cause and extent of this relation as well on the indicated reversibility effects.

1.6 Cocaine use and cognitive functioning: Neuropsychological linkage

Multiple lines of evidence indicate that repeated use of cocaine leads to neuroadaptive changes and dopaminergic alterations mainly exerted in the frontostriatal network. In particular, the orbitofrontal, prefrontal, cingulate, temporoparietal, insular, and cerebellar cortex appear to be affected (Ersche et al., 2011; Franklin et al., 2002; Lim et al., 2008; Matochik et al., 2003; Sim et al., 2007; Volkow et al., 2009; Volkow et al., 2004; Volkow et al., 2007). In all of these areas, cocaine users featured significant grey matter reductions compared with healthy controls (Ersche et al., 2011; Franklin et al., 2002; Lim et al., 2008; Matochik et al., 2003; Sim et al., 2007). Moreover, some of these studies even exhibited a direct link between the duration of cocaine use and grey matter reductions in the orbitofrontal, cingulate, insular, and cerebellar cortex (Ersche et al., 2011; Lim et al., 2008; Sim et al., 2007). By contrast, chronic cocaine users displayed also some substantial enlargements in the striatal structures (Ersche et al., 2011; Jacobsen et al., 2001). Additionally, neuroimaging studies have repeatedly shown that chronic cocaine use is linked to reductions in dopamine D2 receptor availability in the striatum and hence to a decreased dopamine function which is associated with reduced regional metabolic activity in frontal regions such as the orbitofrontal cortex, dorsolateral prefrontal cortex, and cingulate cortex (Volkow et al., 2009; Volkow et al., 2004; Volkow et al., 2007) persisting at least 3 to 4 months after detoxicification (Volkow et al., 1992).

In sum, evidence has accumulated that chronic cocaine use is linked to abnormalities, predominantly in the frontostriatal network. Therefore, cocaine use seems to affect the very same brain areas that are also crucially involved in different aspects of cognitive functioning (Cabeza and Nyberg, 2000; Eagle et al., 2008; Goldstein and Volkow, 2011; Yucel and Lubman, 2007): Whereas the basic attentional

component sustained attention is linked to activations in prefrontal and parietal regions (Cabeza and Nyberg, 2000; Sarter et al., 2001; Stuss and Levine, 2002), working memory processes generally affect prefrontal, parietal and cingulate regions (Cabeza and Nyberg, 2000; Fletcher and Henson, 2001), and the declarative memory seems to rely on a frontotemporal network, mainly exerted in the prefrontal cortex (Cabeza and Nyberg, 2000; Goldstein et al., 2004). Additionally, the prefrontal cortex was found to be involved in most high-level cognitive tasks (Cabeza and Nyberg, 2000) and therefore seems to play a crucial role with regard to the complex and heterogeneous concept of executive functions (Beveridge et al., 2008; Volkow et al., 2012). Furthermore, the prefrontal cortex and the dorsal anterior cingulate cortex are closely linked to trait and behavioral (inhibitory control) impulsivity (Aron, 2011; Eagle et al., 2008; Kramer et al., 2012; Matsuo et al., 2009; Yucel and Lubman, 2007; Zheng et al., 2008). Additionally, repeated cocaine use was clearly connected to impairments in dopamine function, a neurotransmitter system that also plays a critical role in the control of cognition, motivation, reward, and relapse (Martinez et al., 2007; Volkow et al., 1997).

In short, it might be assumed that repeated cocaine use has an impact on cognitive functioning and accordingly leads to cognitive shifts in terms of a pathological usurpation of the neural mechanisms of cognitive functions such as learning and memory (Hyman, 2005), which normally serve to acquire adaptive and hinder maladaptive behavior (Garavan and Hester, 2007; Gould, 2010).

1.7 Research objectives

Altogether, accumulating evidence exists for a strong association between the repeated use of cocaine and alterations in cognitive functions. However, there is still no clarification on the causal relationship as well as on the relation between the extent of cocaine use and the characteristics of cognitive functioning and impulsivity. Furthermore, there is only rudimentary knowledge on how the pattern of cocaine use is linked to changes in cognitive functioning. Therefore, this thesis is designed to help clarify the role of long-term cocaine use with regard to some specific aspects of cognitive functioning. The aim is to capture selective cocaine-related aspects of cognition and impulsivity in a cross-sectional design and to further investigate cognitive functioning by means of a longitudinal study.

In order to examine these issues, we conducted three studies as outlined in chapter 2 to 4. In the first study (chapter 2), we investigated a large cross-sectional sample of recreational cocaine users, dependent cocaine users, and matched stimulant-naïve healthy controls with a comprehensive neuropsychological test battery to examine whether cognitive performance is impaired in relatively pure recreational and dependent cocaine users. In the second study (chapter 3), we analyzed the same study sample with regard to trait and motor impulsivity in relatively pure recreational and dependent cocaine users in order to clarify the role of impulse control in cocaine addiction and non-dependent cocaine use. In the third study (chapter 4), we investigated the relation between changing intensity of

cocaine use and the development of cognitive functioning by means of a 12-months longitudinal study with two test sessions.

As described before, cognitive health in terms of cognitive functioning is closely linked to drug use in general and cocaine use in particular. Accordingly, findings from these studies are intended to give a more detailed insight in the mechanisms of cognitive dysfunction in stimulant users. Accordingly – and particularly because there is currently no effective medication for cocaine addiction (Sofuoglu, 2010) – an extended knowledge on risk factors, aggravating effects, affected brain structures, probable neuroadaptive changes as well as concrete cognitive and behavioral implications is fundamentally important for addiction research, prevention, and intervention.

1.8 The Zurich Cocaine Cognition Study (ZuCo^{2}St)

This thesis was part of the project "Neurosocial consequences of cocaine use: a longitudinal investigation" also referred to as the Zurich Cocaine Cognition Study (ZuCo^{2}St) that was funded by the Swiss National Science Foundation (SNSF) and was carried out under supervision of Prof. Dr. rer. nat. Boris Quednow, head of the Department of Experimental and Clinical Pharmacopsychology at the University Hospital of Psychiatry in Zurich. The ZuCo^{2}St was designed to assess the long-term consequences of cocaine use on different measures of social and non-social cognition, impulsivity, and decision-making.

The data collection focused on the greater area of Zurich and lasted from January 2010 until March 2013. Participants were recruited via advertisements in local newspapers, online media, drug prevention and treatment centers, psychiatric hospitals, and by word of mouth. Out of 1063 requests via email or telephone, 804 potential participants underwent a standardized telephone screening. 240 subjects were considered to be eligible for the first test session at the University Hospital of Psychiatry in Zurich. All subjects were aged between 18 and 60 years and had sufficient German language skills. Because we conducted urine and hair toxicology analyses, we were able to objectively characterize drug use over the past six months. Accordingly, this exclusive and to date unique feature in cocaine research allowed us to investigate a very well described sample with little polytoxic substance. As a consequence, 46 of the 240 participants in the cross-sectional part of the study had to be excluded afterwards due to hair analyses revealing illegal drug use not declared in the self-report interviews of drug use (e.g., opioids, excessive MDMA use), or lack of cocaine use. Therefore, the cross-sectional study sample consisted of 108 cocaine users and 86 control subjects.

For the longitudinal analysis, we conducted a one-year follow-up test session. Six of the 240 participants were not re-invited to participate in the follow-up study because they refused to fully cooperate at the first test session or revealed to have psychiatric disorders or family members with schizophrenia. The remaining 234 participants (138 cocaine users, 96 controls) were contacted and

invited for a follow-up test session twelve months after baseline testing. Whereas 132 participants (56%; 79 cocaine users, 53 controls) agreed to be re-tested, 102 participants were not available for the follow-up study due to different reasons (unattainable, not answering, losing interest, time reasons, death). At follow-up, 27 participants had to be excluded afterwards due to hair analyses revealing illegal drug use not allowed by our exclusion criteria (e.g., opioids, excessive MDMA use) or due to use of psychotropic medication (e.g., antipsychotics, antidepressants).

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2 Cognitive dysfunctions in recreational and dependent cocaine users: The role of ADHD, craving, and early age of onset

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MV collected, analyzed, and interpreted the data and wrote the manuscript. LMH, KHP, and DJ contributed to the data acquisition and/or revised the first draft of the manuscript. MRB conducted the hair analyses. RS contributed to the participant recruitment. KIB revised the first draft of the manuscript. BBQ designed the study, contributed to the data analysis, and revised the manuscript.

2.1 Abstract

Background. Dependent cocaine users consistently display cognitive deficits but cognitive performance of recreational cocaine users has rarely been investigated so far.

Aims. To examine if cognitive performance is impaired in relatively pure recreational and dependent cocaine users.

Method. The cognitive performance of recreational (n=68) and dependent cocaine users (n=30) was compared with the performance of stimulant-naïve controls (n=68) employing an extensive neuropsychological test battery. Moreover, the impact of ADHD symptoms, craving, and early age of onset was analyzed.

Results. Dependent cocaine users display broad cognitive impairments in the domains of attention, working memory, declarative memory, and executive functions. Recreational cocaine users performed in all four domains intermediate between controls and dependent users and displayed significant deficits foremost in the domains attention and working memory. Importantly, ADHD symptoms, craving, and age of onset were important modulators of cognitive function in cocaine users.

Conclusions. Cognitive deficits already occur at a recreational and non-dependent level of cocaine use. Finally, cocaine use and ADHD seem to have mutually aggravating effects on cognitive impairment.

2.2 Introduction

With an annual number of around 4 million users, cocaine is currently the second most frequent illicit drug in Europe (European Monitoring Centre for Drugs and Drug Addiction, 2012). Considering the addictive potential (Nutt et al., 2007; Wagner and Anthony, 2002) and the negative health consequences (Degenhardt, 2012; Nutt et al., 2007), the use of cocaine is still regarded as a major public health issue (Degenhardt, 2012; Nutt et al., 2007).

For more than two decades, research has tried to examine the long-term impact of cocaine by focusing on dependent cocaine users. Evidence has accumulated that addictive cocaine use leads to neuroadaptive changes and dopaminergic alterations mainly exerted in the frontostriatal network (Beveridge et al., 2008; Bolla et al., 2004; Garavan and Hester, 2007; Volkow et al., 2009; Volkow et al., 2004). Imaging studies in chronic cocaine users have repeatedly reported reductions in gray matter density in the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate cortex, and the orbitofrontal cortex (OFC) (Ersche et al., 2011; Franklin et al., 2002; Lucantonio et al., 2012; Matochik et al., 2003; Sim et al., 2007), areas critically involved in several cognitive functions (Cabeza and Nyberg, 2000). Accordingly, cognitive deficits in chronic cocaine users have been linked to structural and functional alterations primarily of the prefrontal cortex (PFC) (Beveridge et al., 2008; Bolla et al., 2004; Garavan and Hester, 2007; Goldstein et al., 2004).

The recent literature is characterized by the consensus that cocaine dependence is associated with significant neuropsychological impairment, while the aetiology and the severity of these impairments are matter of ongoing debate (Beveridge et al., 2008; Goldstein et al., 2004; Jovanovski et al., 2005; Woicik et al., 2009). Existing studies with dependent users indicate persisting cognitive impairments including deficits predominantly in the domains of attention, working and declarative memory, and, less consistently, in the heterogeneous concept of executive functions (Beveridge et al., 2008; Bolla et al., 1999; Cunha et al., 2004; Ersche et al., 2011; Goldstein et al., 2004; Jovanovski et al., 2005; Pace-Schott et al., 2008; Woicik et al., 2009). However, given that these previous studies differed in their inclusion and exclusion criteria regarding comorbid psychiatric diseases, polytoxic drug use history, abstinence time, and verification of self-reported drug intake, the specific impact of chronic cocaine use on cognitive processes was difficult to determine so far.

While most of these studies focused on the chronic misuse of cocaine, relatively little is known about the substantial number of recreational but non-dependent cocaine users (European Monitoring Centre for Drugs and Drug Addiction, 2012). Moreover, in comparison to studies with dependent users, the investigation of recreational users has several advantages, as they are I) not (or not yet) addicted, II) less burdened by psychiatric comorbidities (Smith et al., 2009), III) usually unmedicated with psychotropic drugs, and IV) mostly display less polytoxic drug use. Only recently research has started to systematically investigate possible cognitive effects of recreational cocaine use (Colzato et al., 2009b). Preliminary data from small samples of recreational users indicate that also small and

infrequent doses of cocaine affect different cognitive components such as attention, memory, or components of executive functions (Colzato and Hommel, 2009; Colzato et al., 2009a; Colzato et al., 2007, 2009b; Rahman and Clarke, 2005; Reske et al., 2010b; Soar et al., 2012). However, these previous studies lack a unique definition of recreational cocaine use (recreational cocaine use was either defined by a limited amount of cocaine use or not matching dependency criteria according to DSM-IV criteria), mostly relied on simple self-reported of drug use without objective verification, or tested only very small and predominantly male samples with mainly polytoxic drug use patterns.

As a consequence, after more than two decades of research and despite the supposed public health effects, there is still no clarification on the relation between the extent of cocaine use and the characteristics of cognitive impairments. So far, analyses of regular cocaine users categorized in groups of differing consumption patterns are lacking. Consequently, we aimed to investigate a large sample of recreational users, dependent users, and matched stimulant-naïve healthy controls with a comprehensive neuropsychological test battery to examine if cognitive performance is impaired in relatively pure recreational and dependent cocaine users. Any differences in cognitive performance would have implications notably with regard to risk markers, prevention, and treatment implications (Beveridge et al., 2008; Cunha et al., 2004; Lucantonio et al., 2012). We expect to find considerable cognitive deficits in dependent users and similar but less pronounced cognitive impairments in recreational users, as we recently reported deficits in early information processing and blue-yellow color vision in recreational users suggesting alterations of catecholamine neurotransmission already in recreational users (Hulka et al., 2013b; Preller et al., 2013b). Although psychiatric comorbidities such as Attention-Deficit/Hyperactivity Disorder (ADHD) and depression are frequently present among dependent users (Perez de Los Cobos et al., 2011; Swendsen and Merikangas, 2000), their separate impact on cognition was scarcely investigated so far. Thus, we conducted a comprehensive psychiatric diagnostic interview and additionally assessed symptoms of ADHD and depression with self-report questionnaires. Finally, by performing urine and hair toxicology analyses, we were uniquely able to objectively characterize not only recent drug use but also drug use over the past six months.

2.3 Method

2.3.1 Participants

Sixty-eight recreational cocaine users, 30 dependent cocaine users, and 68 cocaine-naïve control subjects were included in the study (recruitment and selection details **sMethods 1**). The three groups did not differ significantly for age, sex, smoking habits and verbal IQ. Exclusion criteria for all participants were acute or previous neurological disorders or head injury, any clinically significant medical diseases, and use of prescription drugs affecting the CNS. Additional exclusion criteria for the control subjects were all acute or previous Axis I DSM-IV psychiatric disorders including ADHD and any form of addiction except nicotine or regular illegal drug use (>15 occasions lifetime) with exception of occasional cannabis use. Specific exclusion criteria for the cocaine user groups were use of opioids, a polytoxic drug use pattern according DSM-IV, and acute or previous Axis I DSM-IV adult psychiatric disorders with exception of cocaine, cannabis, and alcohol abuse, history of affective disorders (acute major depression was excluded), or ADHD. None of the cocaine users was help-seeking in our department. Inclusion criteria for the two user groups were cocaine as primary drug, cocaine use of >0.5g per month, and an abstinence duration of <6 months. Cocaine dependence was diagnosed according to the Diagnostic and Statistical Manual-IV (DSM-IV) criteria (American Psychiatric Association, 1994), with only dependent users fulfilling these criteria. Participants were asked to abstain from illegal substances for at least 72h and not to consume alcohol 24h before the testing session. Compliance with these instructions was controlled by urine and 6-month hair toxicologies (**sMethods 2**). The study was approved by the Cantonal Ethics Committee of Zurich. All participants provided written informed consent and were compensated for their participation.

2.3.2 Procedure

The present data were collected as part of the longitudinal Zurich Cocaine Cognition Study ($ZuCo^2St$) (Preller et al., 2013b). Trained psychologists conducted a Structured Clinical Interview (SCID-I) (Wittchen et al., 1997) according to DSM-IV procedures. Drug use was assessed by means of a structured and standardized Interview for Psychotropic Drug Consumption (Quednow et al., 2004). For the estimation of verbal intellectual performance, the Mehrfachwahl Wortschatz Intelligenztest (MWT-B) was applied (Lehrl, 1999). The brief version of the Cocaine Craving Questionnaire (CCQ) was used to capture current cocaine craving (Sussner et al., 2006). Smoking habits were assessed by the Fagerstroem Test of Nicotine Dependence (Heatherton et al., 1991). The Beck Depression Inventory (BDI) (Beck et al., 1961) measured the current severity of depression, and the ADHD self-rating scale (ADHD-SR) (Rosler et al., 2004) focused on the diagnosis of ADHD in adulthood according to DSM-IV criteria. Subsequently, participants underwent a comprehensive

neuropsychological test battery as described below. Participants were allowed to take a break at any time and smoking was permitted during the breaks.

2.3.3 Neuropsychological assessment

The test battery comprises four tests of the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Strauss et al., 2006): Rapid Visual Processing (RVP), Spatial Working Memory (SWM), Intra/Extradimensional Set Shifting (IED), Paired Associates Learning (PAL), a German version of the Rey Auditory Verbal Learning Test (RAVLT) (Helmstaedter et al., 2001), and the Letter Number Sequencing Task (LNST) (Wechsler, 1997). With regard to data reduction and specific analyses, 15 predefined main cognitive test parameters were z-transformed on the basis of means and standard deviations of the control group. These parameters were reduced to four in cocaine research commonly used(Goldstein et al., 2004; Jovanovski et al., 2005; Pace-Schott et al., 2008; Woicik et al., 2009) cognitive domains attention, working memory, declarative memory, and executive function according to theoretical a priori considerations (detailed description **sMethods 3**). Furthermore, these four z-scored domains were equally integrated into a global cognitive index (GCI).

2.3.4 Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics 19.0 for Windows (SPSS Inc.). Frequency data were analyzed by means of Pearson's Chi-square test and quantitative data by analyses of variance (ANOVA). Based on significant main effects, Sidak post-hoc comparisons were performed. To control for demographic inequalities, the variables age and verbal IQ were introduced as covariates in analyses of covariance (ANCOVA) with linear group contrasts. Correlation analyses (Pearson's product-moment) to relate drug use parameters to cognitive performance were conducted across a combined user group. Cumulated cocaine use and weekly use in grams were ln-transformed for statistical analyses because of the highly skewed distribution and the resulting deviation from the normal distribution (Shapiro-Wilk $W<.001$). The effect of depression, ADHD, cocaine craving, recent cocaine use (positive urine test), and age of onset on cognitive performance was examined by correlation analyses and ANCOVA subgroup comparisons additionally corrected for severity of cocaine use. The effect of craving status was investigated because previous studies reported that craving for food and nicotine has an impact on cognitive functioning (Kemps and Tiggemann, 2010; Sayette et al., 2010). Multiple logistic regressions were used to estimate odds ratios associated with the use of cocaine and cognitive performance. The odds ratios were left unadjusted because the values decisive for the group assignment were already adjusted for age and verbal IQ.

2.4 Results

2.4.1 Demographic characteristics and drug use

The groups did not differ regarding age, sex distribution, smoking status, and verbal IQ but dependent users had fewer years of education than controls and recreational users (**Table 1**). As expected, dependent users displayed higher BDI and ADHD-SR sum scores than controls and recreational users, while recreational users showed higher scores than controls.

Table 1. Demographic Data

	Stimulant-naïve controls	Recreational cocaine users	Dependent cocaine users	Value[a]	df, df_{err}	p
N	68 (41%)	68 (41%)	30 (18%)			
Age, y	30.3 (9.2)	28.7 (6.2)	32.5 (9.0)	F=2.386[a]	2, 163	.10
Sex (f/m)	21 / 47	18 / 50	8 / 22	x^2=0.375[b]	2	.83
Smoking (y/n)	53 / 15	53 / 15	24 / 6	x^2=0.061[b]	2	.97
Verbal IQ (MWT-B)	104.4 (9.7)	103.2 (9.6)	99.7 (9.1)	F=2.457[a]	2, 163	.09
School education, y	10.7 (1.8)	10.5 (2.0)	9.5 (1.2)**°	F=4.822 [a]	2, 163	**.01**
BDI sum score (0-63)	4.6 (4.4)	7.4 (6.1)*	11.8 (8.6)***°°	F=15.009 [a]	2, 163	**<.001**
BDI depression status (y/n)[d]	5 / 63	17 / 51	12 / 18	x^2=15.066[b]	2	**<.001**
ADHD-SR sum score (0-22)	7.6 (4.8)	13.2 (9.0)***	17.1 (8.7)***°	F=19.517 [a]	2, 163	**<.001**
ADHD DSM IV (y/n)[e]	0 / 68	14 / 54	8 / 22	x^2=18.266[b]	2	**<.001**
Craving for cocaine (0-70)	-	19.0 (9.1)	20.3 (11.4)	T=0.598[c]	1, 96	.55

Means and standard deviations. Significant p values are shown in bold. Sex, smoking, BDI depression status, and ADHD-SR DSM-IV are shown in frequency data.
[a] ANOVA (all groups), [b] χ^2 test (all groups) for frequency data, or [c] independent t-test (cocaine users only).
[d] BDI, Beck Depression Inventory (cut-off ≥11).
[e] ADHD-SR, ADHD self rating scale (cut-off DSM-IV criteria).
* Significant Sidak post-hoc test vs. control group: *p<.05; **p<.01; ***p<.001.
° Significant Sidak post-hoc test vs. RCU group: °p<.05; °°p<.01.

As strived for, hair samples revealed a clear domination of cocaine compared to other illegal drugs (**Table 2**), whereby dependent users showed a more than 8-fold higher concentration of cocaine and metabolites compared to recreational users. Nonetheless, recreational users were regular users with a mean weekly consumption of about 1g of cocaine but without fulfilling the DSM-IV criteria for dependence (41 recreational users met the criteria for cocaine abuse). The main route of administration was intranasal, only three dependent users were primarily inhaling the drug (2 free-base, 1 coca paste). In the urine samples, 10 recreational and 12 dependent users tested positive for cocaine. However, we decided not to exclude them but to investigate the acute and post-acute effects of the drug.

Table 2. Pattern and amount of drug use

	Stimulant-naïve controls (n=68)	Recreational cocaine users (n=68)	Dependent cocaine users (n=30)
Alcohol			
Grams per week[a]	116.8 (122.6)	167.8 (117.5)	188.5 (260.6)
Years of use	13.2 (9.3)	11.2 (5.1)	13.5 (9.5)
Nicotine			
Cigarettes per day[a]	9.3 (9.5)	11.7 (8.8)	15.7 (13.5)
Years of use	9.2 (9.2)	9.6 (6.4)	14.2 (9.3)
Cocaine			
Times per week[a]	-	1.1 (1.0)	2.9 (2.6)
Grams per week[a]	-	1.1 (1.4)	7.9 (15.8)
Years of use	-	6.5 (4.0)	9.4 (6.5)
Maximum dose (grams/day)	-	3.5 (2.5)	9.4 (8.4)
Cumulative dose (grams)	-	519.7 (751.2)	5500.9 (9635.2)
Last consumption (days)[b]	-	27.5 (37.6)	21.0 (33.6)
Hair analysis Cocaine pg/mg[c]	-	2739 (4628)	22164 (32609)
Hair analysis Benzoylecgonine pg/mg[c]	-	546 (919)	5048 (7711)
Hair analysis Cocaethylene pg/mg[c]	-	276 (316)	2006 (3656)
Hair analysis Norcocaine pg/mg[c]	-	62 (101)	586 (758)
Hair analysis $Cocaine_{total}$ pg/mg[c,e]	-	3347 (5580)	27798 (40226)
Urine toxicology (neg/pos)[d]	68 / 0	57 / 10	18 / 12
Cannabis			
Grams per week[a]	0.5 (1.0)	0.9 (2.1)	1.2 (3.7)
Years of use	4.7 (6.5)	7.7 (6.0)	10.5 (9.9)
Cumulative dose (grams)	358.3 (846.2)	1042.8 (1780.0)	3550.3 (5959.0)
Last consumption (days)[b]	36.2 (50.1); n=33	22.1 (32.3); n=44	25.7 (32.8); n=20
Urine toxicology (neg/pos)[d]	58 / 10	55 / 12	20 / 10
Amphetamine			
Grams per week[a]	0.0 (0.0)	0.1 (0.2)	0.0 (0.2)
Years of use	0.0 (0.1)	1.6 (3.0)	1.5 (3.2)
Cumulative dose (grams)	0.2 (1.4)	21.2 (56.8)	22.3 (62.8)
Last consumption (days)[b]	121.6 (0.0), n=1	61.8 (51.3); n=25	78.4 (75.4); n=6
Hair analysis Amphetamine pg/mg[c]	1 (7)	76 (257)	60 (169)
MDMA			
Tablets per week[a]	-	0.1 (0.3)	0.4 (1.8)
Years of use	0.3 (1.7)	2.5 (3.8)	3.1 (5.2)
Cumulative dose (tablets)	0.9 (2.9)	35.9 (90.5)	157.4 (393.5)
Last consumption (days)[b]	-	75.1 (84.8); n=20	82.1 (45.4); n=9
Hair analysis MDMA pg/mg[c]	3 (16)	545 (1598)	255 (653)
GHB			
Cumulative dose (pipettes)	0.0 (0.0)	1.8 (9.5)	1.3 (2.9)
Hallucinogens			
Cumulative dose (times)	0.9 (2.2)	6.0 (14.6)	6.9 (11.8)

Means and standard deviations. Use frequency, duration of use, and cumulative doses are averaged within the total group.
[a] Average use during the last 6 months.
[b] Last consumption is averaged only for persons who consumed in the last 6 months. In this case, sample size (n) is shown.
[c] Cut-off values for cocaine = 500 pg/mg and for amphetamines/MDMA = 200 pg/mg (Cooper et al., 2012). Hair samples were voluntary and are deficient for 3 controls and 1 RCU.
[d] Cut-off values for cocaine = 150 ng/ml and for Tetrahydrocannabinol 50 ng/ml (Substance Abuse and Mental Health Services Administration, 2008). Urine toxicology test was deficient for 1 RCU.
[e] $Cocaine_{total}$ (= Cocaine + Benzoylecgonine + Norcocaine) is a more robust procedure for discrimination between incorporation and contamination of hairs (Hoelzle et al., 2008).

2.4.2 Neurocognitive measures

The ANCOVA for the GCI showed a significant group effect including a clear linear trend (p<.001), and significant pairwise comparisons between all three groups (**Table 3; Figure 1; sFigure 1**), indicating global cognitive impairment in both cocaine user groups. Likewise, all four domains (p<.001) and 12 of 15 test parameters (p<.05-.00001, except the two IED parameters and the SWM strategy score) displayed significant linear trends, suggesting robust dose-response relationships. In all domains, recreational and dependent users differed significantly from controls. Additionally, the domains working memory and executive functions showed significant group differences between recreational and dependent users. The single test parameters within the attention, working memory, and declarative memory domains (detailed RAVLT analysis **sFigure 2)** showed similar results. However, the effect in the executive function domain was mainly driven by a strong effect regarding RAVLT recall consistency and, to a lesser degree, by the SWM strategy score, whereas the two IED parameters did not show any substantial group differences (detailed IED analysis **sFigure 3**).

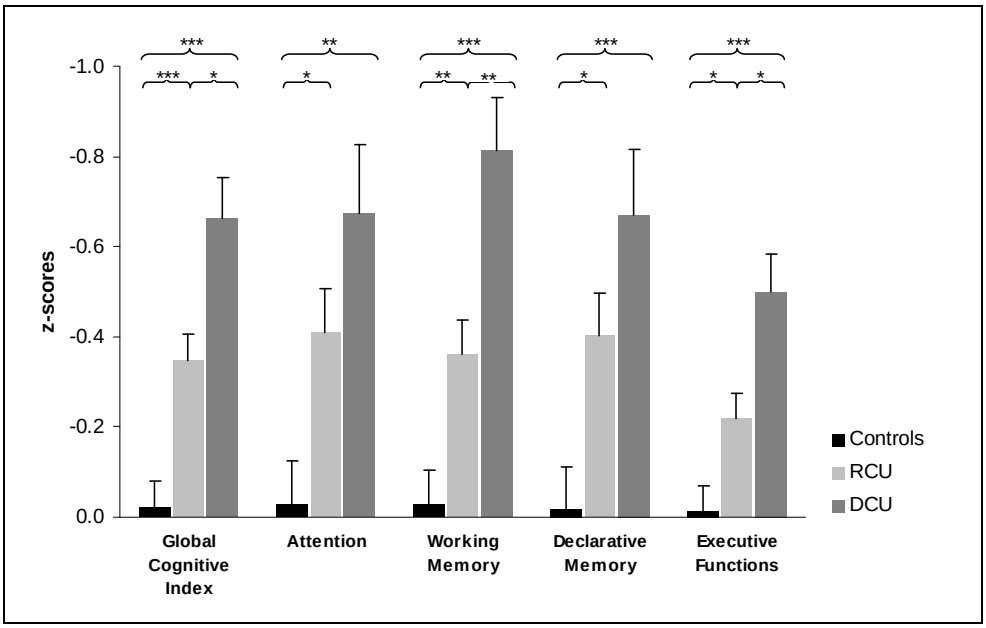

Figure 1. Mean z-scores and standard errors for the global cognitive index (GCI) and the four cognitive domains (values corrected for age and verbal IQ). Sidak post-hoc tests: *p<.05; **p<.01; ***p<.001.

Table 3. Neurocognitive global and domain z-scores and scores of neuropsychological tests

Measure	n[a]	Stimulant-naïve controls	Recreational cocaine users	Dependent cocaine users	F	df, df_{err}	p	p, Sidak post-hoc: Controls vs. RCU	p, Sidak post-hoc: Controls vs. DCU	p, Sidak post-hoc: RCU vs. DCU	Cohen's d: Controls vs. RCU	Cohen's d: Controls vs. DCU	Cohen's d: RCU vs DCU
Global Cognitive Index	68/68/30	-0.02 (0.06)	-0.35 (0.06)	-0.67 (0.09)	19.345	2, 161	**<.001**	**<.001**	**<.001**	**.01**	0.53	1.04	0.52
Neurocognitive domain scores													
Attention	68/68/30	-0.03 (0.10)	-0.41 (0.10)	-0.68 (0.15)	7.579	2, 161	**<.001**	**.02**	**.001**	.38	0.44	0.74	0.30
Working memory	68/68/30	-0.03 (0.08)	-0.36 (0.08)	-0.81 (0.12)	16.312	2, 161	**<.001**	**.007**	**<.001**	**.005**	0.43	1.00	0.58
Declarative memory	68/68/30	-0.02 (0.09)	-0.4 (0.09)	-0.67 (0.15)	8.333	2, 161	**<.001**	**.01**	**<.001**	.34	0.43	0.73	0.30
Executive functions	68/68/30	-0.02 (0.06)	-0.22 (0.06)	-0.5 (0.09)	11.388	2, 161	**<.001**	**.03**	**<.001**	**.02**	0.39	0.92	0.54
Neuropsychological test scores													
Attention													
RVP Discrimination performance A'	67/68/30	0.917 (0.0)	0.899 (0.0)	0.885 (0.0)	6.254	2, 160	**.002**	**.04**	**.004**	.43	0.42	0.72	0.31
RVP Total hits	67/68/30	18.3 (0.5)	16.5 (0.5)	15.3 (0.8)	5.561	2, 160	**.005**	**.05**	**.008**	.53	0.40	0.67	0.27
RAVLT Supraspan trial 1	68/68/30	8.9 (0.2)	8.4 (0.2)	8.0 (0.4)	2.407	2, 161	.09	.31	.13	.81	0.25	0.41	0.17
Working memory													
LNST Score	68/68/30	15.6 (0.3)	14.5 (0.3)	13.2 (0.5)	8.320	2, 161	**<.001**	.07	**<.001**	.07	0.34	0.78	0.44
SWM Total errors	68/67/30	20.1 (1.9)	23.3 (1.9)	34.5 (2.9)	8.727	2, 160	**<.001**	.53	**<.001**	**.005**	0.19	0.84	0.65
PAL First trial memory score	68/67/30	15.6 (0.4)	14.1 (0.4)	13.4 (0.6)	6.575	2, 160	**.002**	**.02**	**.005**	.67	0.43	0.64	0.21
Declarative memory													
RAVLT Learning performance (? trials 1-5)	68/68/30	62.0 (0.9)	58.0 (0.9)	54.9 (1.4)	9.612	2, 161	**<.001**	**.009**	**<.001**	.22	0.45	0.80	0.35
RAVLT Adjusted recognition perf. p(A)	68/68/30	0.873 (0.0)	0.858 (0.0)	0.823 (0.0)	2.076	2, 161	.13	.83	.12	.39	0.13	0.44	0.31
RAVLT Delayed recall trial 7	68/68/30	13.1 (0.3)	11.9 (0.3)	11.4 (0.5)	6.046	2, 161	**.003**	**.02**	**.009**	.75	0.44	0.63	0.19
PAL Total errors adjusted	68/67/30	10.6 (1.4)	15.1 (1.4)	16.9 (2.2)	3.852	2, 160	**.02**	.08	.05	.88	0.35	0.49	0.14
PAL Total trials adjusted	68/67/30	8.5 (0.3)	9.5 (0.3)	10.1 (0.5)	4.231	2, 160	**.02**	.09	**.03**	.72	0.34	0.53	0.19
Executive functions													
IED Total errors adjusted	68/68/30	30.3 (4.1)	31.3 (4.1)	32.3 (6.3)	.039	2, 161	.96	1.00	.99	1.00	0.03	0.06	0.03
IED Total trials adjusted	68/68/30	104.1 (7.2)	107.3 (7.3)	108.5 (11.2)	.075	2, 161	.93	.98	.98	1.00	0.05	0.07	0.02
SWM Strategy score	68/67/30	32.7 (0.6)	33.4 (0.6)	34.9 (0.9)	1.887	2, 160	.15	.84	.15	.43	0.12	0.42	0.30
RAVLT Recall consistency in %	68/68/30	92.3 (1.1)	88.1 (1.1)	83.3 (1.6)	11.004	2, 161	**<.001**	**.02**	**<.001**	**.05**	0.43	0.92	0.49

Means and standard errors. ANCOVA (all groups, corrected for age and verbal IQ). Significant p values are shown in bold. GCI and cognitive domain scores are z-transformed values.
The robustness of these parametric tests was confirmed using bootstrap simulations with 1000 replications. Thereby, only one pairwise Sidak post-hoc comparison above turned from a significant group difference into a statistical trend (RAVLT recall consistency; cocaine rec vs. cocaine dep $p_{post\text{-}hoc}$=.08).
[a] Sample size control group/RCU/DCU. In each of the tasks RVP, PAL, and SWM one subject is missing due to a technical failure.

Correlation analyses within the total group of cocaine users (n=98) revealed that the GCI and the domains working memory, declarative memory and executive functions were all inversely associated with cumulative cocaine dose, duration of cocaine use, cocaine metabolites benzoylecgonine and norcocaine in the hair, and a composite index reflecting the severity of cocaine use (**Table 4**; intercorrelation of cocaine use parameters **sTable 1**). Interestingly, the domain attention was only strongly correlated with the cumulative cocaine dose. The relatively high correlations in the domain executive functions were again driven by both the RAVLT and SWM parameter, while no associations were found for the two IED measures (single test correlation analysis **sTable 2)**.

Table 4. Correlations between cognitive global and domain z-scores and cocaine use parameters in cocaine users

	n	Global Cognitive Index	Attention	Working memory	Declarative memory	Executive functions
Cumulative dose (grams) log[a]	98	***-.50	**-.31	***-.39	***-.43	***-.42
Cumulative dose (grams) log, adj. for age[b]	98	***-.47	***-.34	***-.34	***-.39	***-.37
Times per week[a]	98	-.17				*-.25
Grams per week log[a]	98					
Years of use[a]	98	***-.33		***-.33	**-.29	***-.40
Years of use, adj. for age[b]	98	**-.28		*-.25	*-.22	***-.35
Maximum dose (grams/day)[a]	98	**-.26	*-.23		**-.27	
CCQ sum score (0-70)[a]	98			-.18		
Hair analysis Cocaine pg/mg[a]	97[c]	*-.22			-.20	-.18
Hair analysis Benzoylecgonine pg/mg[a]	97[c]	**-.29	-.17	*-.24	**-.28	*-.20
Hair analysis Cocaethylene pg/mg[a]	97[c]					
Hair analysis Norcocaine pg/mg[a]	97[c]	**-.28		**-.26	**-.27	*-.21
Hair analysis $Cocaine_{total}$ pg/mg[a]	97[c]	*-.24		-.17	*-.22	-.19
Severity of cocaine use Index[a,d]	98	***-.40	*-.21	**-.28	***-.37	***-.42

Correlations with a p-level below 10% are shown, while significant correlations are marked: *p<.05; **p<.01; ***p<.001
[a] Pearson's product-moment correlation.
[b] Partial Correlation corrected for age.
[c] Hair samples were voluntary and are deficient for 1 RCU.
[d] Severity of cocaine Index use corresponds to the mean of the z-transformed parameters cumulative dose, grams per week, years of use, maximum dose, and hair analysis $Cocaine_{total}$.

2.4.3 ADHD, age of onset, craving, depression, and acute drug effects

Analysis of ADHD and craving subgroups by further splitting user groups according to predefined criteria (Rosler et al., 2004) (yes/no fulfilling DSM-IV criteria in ADHD-SR) or median split (low/high, CCQ ≤16) suggested an impact of these variables on cognitive performance (**Figure 2**). ANCOVAs showed significant group effects for ADHD ($F(4,158)=9.56$, $p<.001$) and craving subgroups ($F(4,158)=9.35$, $p<.001$). While presence of craving additionally decreased cognitive performance only in recreational users ($d=.26$)(**Figure 2b**), an ADHD diagnosis had a detrimental effect on cognitive functioning in both, recreational ($d=.30$) and dependent users ($d=.33$)(**Figure 2a**). Notably, recreational and dependent users without ADHD still significantly differed from controls. A combined analysis of ADHD and craving status in an integrated group of cocaine users confirmed this assumption by revealing a significant main effect for group ($F(4,158)=7.66$, $p<.001$), whereby the controls differed significantly from all cocaine user groups (**Figure 2c**). Age of onset of cocaine use played a crucial role ($F(2,160)=10.92$, $p<.001$), as users starting cocaine use before the age of 19 years performed significantly worse than users with a later age of onset ($d=.66$), whereby both users groups differed substantially from the control group ($d_{\leq 18}=1.10$, $d_{>18}=.43$)(**Figure 3**).

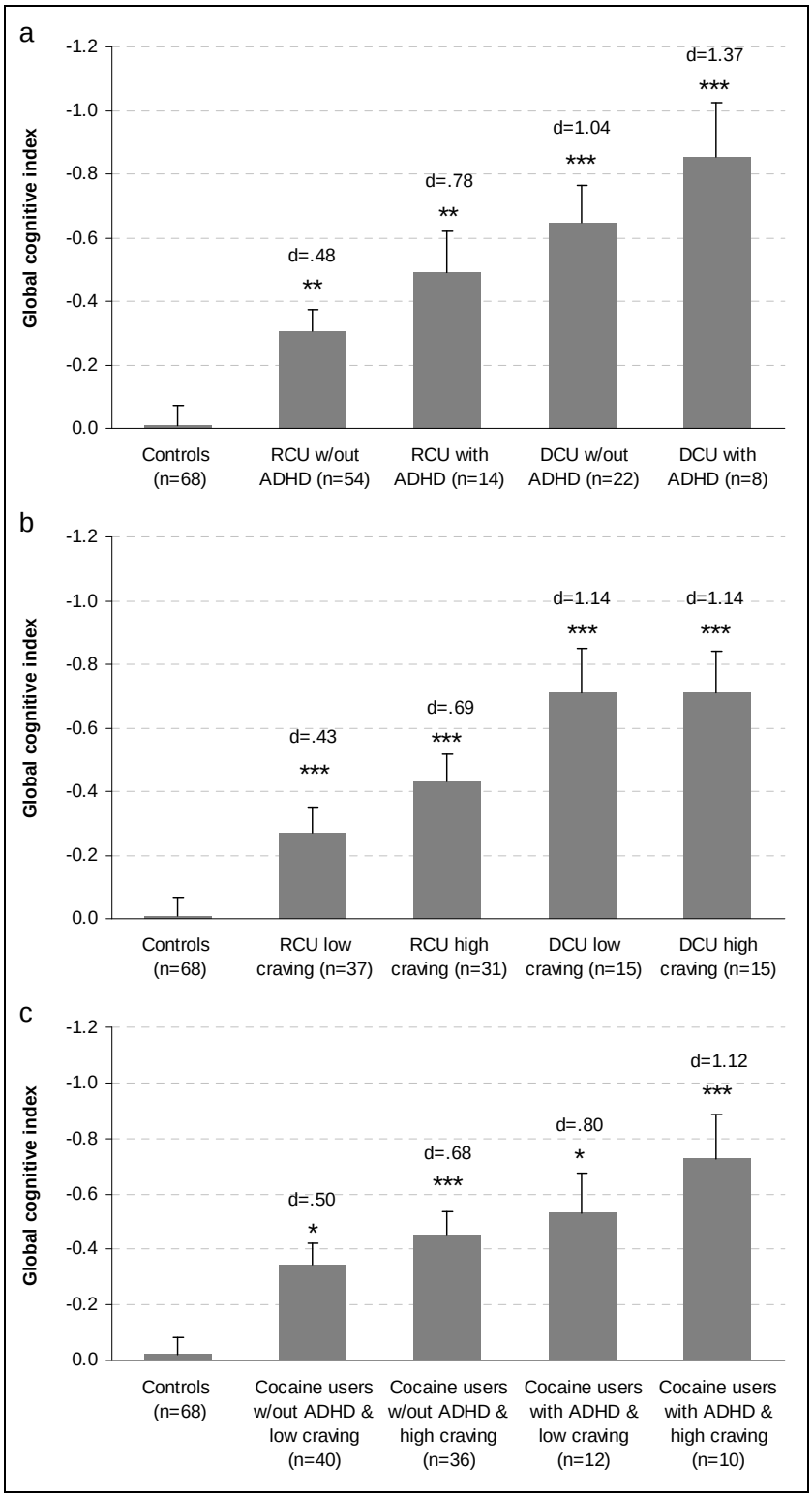

Figure 2. Mean global cognitive index (GCI) scores and standard errors in groups stratified for cocaine use and confounding variables (values corrected for age, verbal IQ, and cocaine gram/week). Significant Sidak post-hoc test vs. control group: *p<.05; **p<.01; ***p<.001. Cohen's d vs. control group. **(a)** ADHD, DSM-IV criteria based on ADHD-SR. **(b)** CCQ, craving for cocaine status based on median split ≤16. **(c)** Combined user group (n=98) stratified for ADHD, DSM-IV criteria based on ADHD-SR and CCQ, craving for cocaine status based on median split ≤16.

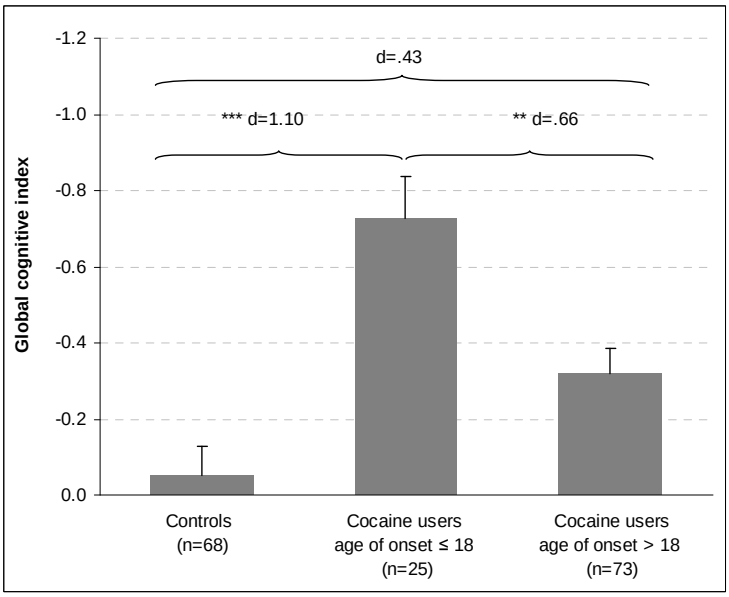

Figure 3. Mean GCI scores and standard errors in groups stratified for age of onset for cocaine use (values are corrected for age, verbal IQ, and cocaine use in years). Group sizes (n) are shown. Significant Sidak post-hoc test vs. reference control group: **p<.01; ***p<.001.

Splitting the user groups and controls according to a predefined depression criterion (Hautzinger et al., 1994) (low/mild≤, BDI ≥11) showed a significant group effect ($F(5,157)=7.41$, $p<.001$) reflecting a weak additive impact of depressive symptoms on cognitive performance only in recreational users ($d=.28$). Again, also non-depressed cocaine users differed significantly from non-depressed controls (**sFigure 4)**.

To test the influence of recent cocaine use, cocaine users were divided into users with positive (n=22, range: 217-24'888ng/ml, mean: 3'873ng/ml, SD: 6'461ng/ml) and users with negative urine samples (n=75) and compared with controls (n=68). Results revealed significant group effects for the GCI ($F(2,160)=14.76$, $p<.001$). Pairwise Sidak-comparisons yielded still significant and relatively strong differences between controls and both user groups ($d_{neg}=.63$, $d_{pos}=.84$), whereas users with positive urine sample showed slightly but non-significantly lower GCI scores than users with negative urine samples ($d=.22$). Similar patterns were found for all four domains (**sFigure 5**).

Multiple regression analyses conducted only in cocaine users confirmed that cumulative dose and duration of cocaine use were the best predictors of cognitive performance in contrast to psychopathological symptoms (**sTable 3**).

2.4.4 Risk threshold for cognitive impairments

As the use of cocaine proved to be an important determinant for cognitive performance, odds ratios were calculated to assess the risk for impairment when using cocaine. If a progressive clinical criterion of -1 SD was applied to define a cognitive decline, the use of cocaine indicated significant relative risks for deficits in attention (*OR*=3.52, *95% CI*=1.60-7.72, $p<.01$), working memory (*OR*=3.08, *95%*

CI=1.47-6.49, *p*<.01), declarative memory (*OR*=2.40, *95% CI*=1.11-5.19, *p*<.05), and executive functions (*OR*=3.28, *95% CI*=1.53-7.04, *p*<.01). In summary, cocaine users were 3.8 times more likely to manifest global cognitive deficits (GCI) than controls (*OR*=3.80, *95% CI*=1.81-7.97, *p*<.001). If a conservative clinical criterion of -2 SD was applied, 1.5% (n=1) of the controls, 11.8% (n=8) of the recreational users, and 30% (n=9) of the dependent users revealed strong global cognitive impairment. Additionally, **Figures 4a,b** illustrated a clearly increasing risk of cognitive impairment by increasing cumulative doses of cocaine. While this analysis emphasized the long-term impact of cocaine use for all four cognitive domains, declarative memory is the latest, whereas working memory is generally the earliest and most affected domain. Interestingly, a consumption of more than 1kg cocaine lifetime seemed to strongly enhance the risk for cognitive impairment (**Figure 4a**), while a consumption of more than 100g lifetime was associated with a ~50% risk for mild cognitive impairment (**Figure 4b**).

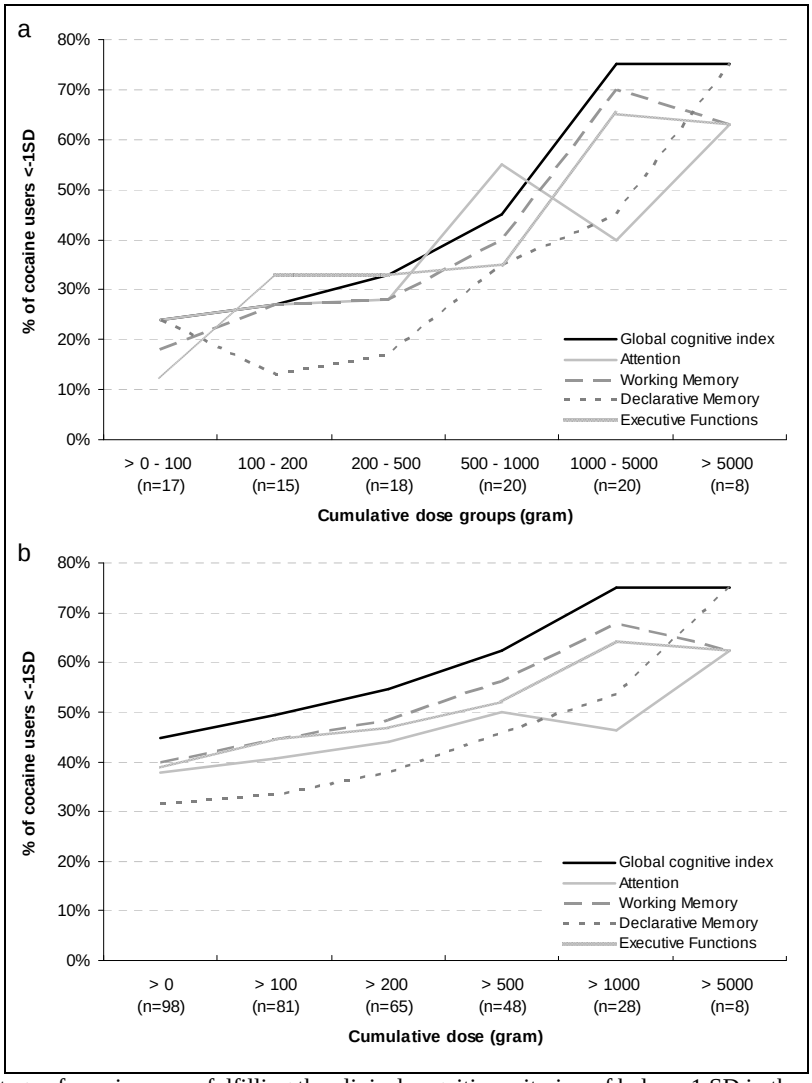

Figure 4. (a) Percentage of cocaine users fulfilling the clinical cognitive criterion of below -1 SD in the specific cumulative dose group. **(b)** Percentage of cocaine users fulfilling the clinical cognitive criterion of below -1 SD in groups with from left to right ascending cumulative doses. Domain cut-offs: GCI SD=-.54, Attention SD=-.81, Working memory SD=-.70, Declarative memory SD=-.82, Executive functions SD=-.38. Values are corrected for age and verbal IQ.

2.5 Discussion

The aim of the present study was to examine whether cognitive performance is impaired in recreational and dependent cocaine users. In contrast to previous studies, hair toxicologies and comprehensive psychiatric diagnostics allowed the investigation of relatively pure cocaine users with little psychiatric comorbidity. Moreover, this is the largest published sample of neuropsychologically examined cocaine users so far (n=98) and the first study directly comparing the cognitive performance of stimulant-naïve controls with both, recreational and dependent users. The major finding of the present study is that intensive recreational showed small but significant cognitive dysfunction further deteriorating in dependent users. Recreational users displayed the strongest effects in the attention domain, while in dependent users working memory was most affected. Correlation and regression analyses revealed negative associations between cognitive performance and cocaine metabolites in the hair, cumulative cocaine dose, and duration of cocaine use suggesting that cognitive impairments might be partially cocaine-induced. Additionally, the influence of ADHD and cocaine craving on cognitive functioning of cocaine users was not systematically investigated before, a shortcoming that we overcame here. We found that symptoms of ADHD and depression as well as craving for cocaine are important modulators of cognitive function in cocaine users, whereas recent cocaine use seemed to be less important. However, cognitive dysfunction is still present in cocaine users without presence of craving, depression, or ADHD symptoms. Finally, we could demonstrate that the risk for cognitive impairment increases with early age of onset and ascending cumulative cocaine doses in particular if estimated lifetime doses of 500g to 1kg cocaine are exceeded (**Figure 4**).

The present results indicate impaired attention in both, recreational and dependent users, with moderate to strong effect sizes, respectively. As attention involves several subprocesses, it should be emphasized that our domain is primarily based on two RVP parameters measuring sustained attention. Therefore, we replicated previous reports on sustained attention deficits in dependent users (Jovanovski et al., 2005; Pace-Schott et al., 2008) but extends the current knowledge regarding relatively pure recreational users, as attentional deficits have previously been indicated only in small samples (n=13-18) of polytoxic recreational users (Colzato and Hommel, 2009; Colzato et al., 2009b; Soar et al., 2012).

Concerning working memory, the strong effect sizes found for dependent users confirm previous findings also mostly drawn from much smaller samples (Jovanovski et al., 2005; Woicik et al., 2009). Also in accordance with a recent study investigating a small sample of polydrug recreational users (n=17), we found that recreational cocaine use is associated with subtle visuo-spatial working memory impairment (Soar et al., 2012). Our results are the first to indicate small to moderate verbal working memory deficits in recreational users.

Furthermore, we confirmed consistently revealed broad deficits of verbal (Cunha et al., 2004; Goldstein et al., 2004; Pace-Schott et al., 2008) and visual learning and memory (Cunha et al., 2004; Goldstein et al., 2004; Jovanovski et al., 2005) in dependent users. The only report analyzing recreational users described similar verbal memory deficits for recreational prescription stimulant users with >80% cocaine co-use, but found no significant effects in a small group (n=13) of recreational users with a low minimal inclusion threshold (three uses in past 6 months) (Reske et al., 2010b). Thus, declarative memory dysfunction is associated not only with chronic, but also with recreational cocaine use. However, compared to other domains declarative memory seemed to be least affected at cumulative cocaine doses <500g.

Unlike in the other domains, the single executive function parameters displayed inconsistent results. Both IED parameters indicated no performance deficits in the user groups. On the contrary, the SWM strategy score demonstrated small to moderate, and the RAVLT recall consistency moderate to strong effects in recreational and dependent users. These inconsistencies are typical for the heterogeneous concept of executive functions reflecting varying task requirements and difficulty levels between studies (Jovanovski et al., 2005). Nevertheless, the existing literature reported executive deficits in dependent users rather on complex than on simple tasks (Jovanovski et al., 2005). As 71% of the subjects in the user groups achieved the highest IED stage, a ceiling effect can be assumed. Furthermore, we found strong correlations between the executive domain and several cocaine use parameters confirming similar relationships that were found in earlier studies on dependent (Bolla et al., 1999) and recreational users (Colzato et al., 2007).

Sustained attention and working memory processes are both associated with increased activity in prefrontal, parietal, and cingulate brain regions (Cabeza and Nyberg, 2000). Accordingly, the LNST involves the lateral PFC (Yochim et al., 2007), the SWM performance is associated with the DLPFC and VLPFC (Manes et al., 2002; Owen et al., 1996), and the PAL depends on frontal and medial temporal lobe function (Owen et al., 1995). In depths analysis of the RAVLT revealed that cocaine users primarily display learning and retrieval deficits, while recognition was less affected – a pattern specifically reported for PFC lesions (Janowsky et al., 1989). Likewise, PCF lesions have been related to impairments in recall consistency (Alexander et al., 2003; Benedict et al., 2005). Finally, glucose metabolism in the DLPFC significantly predicted visual and verbal memory performance in cocaine addicted subjects and controls (Goldstein et al., 2004). Together with previous findings that dependent users display decreased gray matter volume and glucose metabolism in the OFC and DLPFC (Ersche et al., 2011; Ersche et al., 2012a; Ersche et al., 2012b; Franklin et al., 2002; Lucantonio et al., 2012; Matochik et al., 2003; Sim et al., 2007; Volkow et al., 1991; Volkow et al., 1992) the neuropsychological profile therefore suggests that similar but less pronounced alterations of the PFC might be present in recreational users.

We investigated potential co-factors frequently associated with cocaine use or commonly addressed as confounding factors for cognition such as ADHD and depressive symptoms (Gotlib and Joormann, 2010; Perez de Los Cobos et al., 2011). Moreover, craving for food (Kemps and Tiggemann, 2010) and nicotine (Sayette et al., 2010) has been shown to have an impact on cognitive functioning but the specific impact of cocaine craving has not been investigated so far. Here, high craving and depression scores or an ADHD diagnosis further decreased the cognitive performance within the group of recreational users. Additionally, dependent users with clinically relevant ADHD symptoms displayed stronger cognitive deficits (d=1.37) than dependent users without ADHD (d=1.04), while neither craving nor depression symptoms had an additional effect in this group. Importantly, cocaine users without clinically relevant ADHD or depression scores and also with low craving scores still displayed significant cognitive deficits, whereas a combination of an ADHD diagnosis and high craving lead to the strongest impairments, similar to our results on early information processing (Preller et al., 2013b). Regarding the impact of depression, our findings confirm a previous result reporting no additional effect of dysphoria on cognitive performance in a sample of predominantly dependent users (Woicik et al., 2009) but our data additionally indicate a small impact of depression at a recreational level of use.
ADHD is characterized by problems in attentional performance and inhibitory control and patients with ADHD on average perform worse than healthy controls on tests of attention and executive function (Valera et al., 2010). Nevertheless, the influence of ADHD symptoms on the cognition of cocaine users, in which ADHD is highly prevalent, was not investigated so far. The exact pathogenesis underlying ADHD is still unknown (Shen et al., 2012), but as abnormalities within catecholamine systems and the PFC seem to play a major role in ADHD (Liston et al., 2011; Shen et al., 2012) and cocaine use (Volkow et al., 2009; Volkow et al., 2004), it can be assumed that similar pathologies might lead to a mutual aggravation of detrimental effects on cognitive performance.
In contrast to a previous finding, showing that cocaine users with a positive urine toxicology have slightly improved cognitive performances (Woicik et al., 2009), users with positive cocaine urine tests displayed only slightly worse cognitive scores in the present study. As urine toxicologies were performed by immunoassays, which are only presumptive and potentially biased by external factors (Moeller et al., 2008), positive urine tests do not necessarily proof a violation of the requested three day cocaine retention period.

The study has some limitations: I) Cocaine dependency was diagnosed according to the DSM-IV criteria (American Psychiatric Association, 1994). These criteria depend on introspection and self-report but do not consider features such as duration and amount of cumulative doses. Thus, some subjects in the recreational users group might be misclassified as non-dependent. II) Although this is one of the first investigations employing hair analysis in a neurocognitive study with cocaine users, we can only rely on self-reports for all illegal drug use prior to 3 to 6 months (depending on hair length). This is, however, an inevitable constraint of all studies with illegal drug users (Curran, 2000). III) A

cross-sectional design cannot determine whether these cognitive deficits in cocaine users are preexistent traits (vulnerability or resilience), drug-induced consequences, or both. Hence, to answer this question we need to await the findings of the second part of the ZuCo^2 longitudinal study in 2013. IV) As cocaine users participating voluntary in a study session lasting several hours feature a certain level of motivation and cognitive functionality, we assume that the cocaine users in our sample are not the most impaired subjects and probably even perform relatively well. Thus, the cognitive impairments shown here might partially be underestimated for both, recreational and dependent users.

The results confirmed that dependent cocaine use is associated with broad cognitive impairments in the domains attention, working memory, declarative memory, and parts of the executive functions. In all four domains, recreational users performed intermediate between controls and dependent users and displayed significant deficits predominantly in the domains attention and working memory, which is in line with our previous work indicating catecholamine dysfunction already at a recreational level of use (Hulka et al., 2013b; Preller et al., 2013b). Furthermore, all cognitive domains displayed correlations with the long-term intake parameters duration and amount of cocaine use and specifically early age of onset was linked to considerable cognitive dysfunction. The neuropsychological profile suggests PFC dysfunction as the common denominator of these cognitive impairments, which is in line with previous findings showing alterations of the frontostriatal dopamine system in addicted cocaine users (Bolla et al., 2004; Ersche et al., 2012a; Ersche et al., 2012b). Additionally, cocaine use and ADHD seem to have mutually aggravating effects on cognitive impairments. Altogether these results indicate gradual impairments in both, recreational and dependent cocaine users, while clinically relevant cognitive deficits seem to arise with long-term cocaine use as best reflected by cumulative cocaine dose.

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2.7 Supplementary material

2.7.1 Methods

sMethods 1: Recruitment and selection

The recruitment focused on the greater area of Zurich and lasted from January 2010 until January 2012. Participants were recruited via advertisements in local newspapers, online media, drug prevention and treatment centers, psychiatric hospitals, and by word of mouth. Eight-hundred-four prospective participants underwent a standardized telephone interview, whereof 240 subjects were considered to be eligible for the study at the University Hospital of Psychiatry in Zurich. All subjects were aged between 18 and 60 years and had sufficient German language skills. Forty-six participants had to be excluded afterwards due to hair analyses revealing illegal drug use not declared in the interviews (e.g., opioids, excessive MDMA use), or lack of cocaine use. Furthermore, the data of four participants (3 controls, 1 cocaine user) could not be analyzed because of technical problems during the test session and 24 participants were excluded due to matching reasons (age, verbal IQ, and smoking) between groups (15 controls, 9 cocaine users). Hair samples were provided by 163 subjects, as hair analysis was not possible due to an insufficient amount of hair for two controls and one cocaine user.

sMethods 2: Urine and heir toxicologies

Urine toxicology analyses comprised the compounds/substances: tetrahydrocannabinol, cocaine, amphetamines, benzodiazepines, opioids, and methadone and were assessed by a semi-quantitative enzyme multiplied immunoassay method using a Dimension RXL Max (Siemens, Erlangen, Germany).

To characterize drug use over the last six months objectively, hair samples were collected and analyzed with Liquid chromatography-tandem mass spectrometry (LC-MS/MS). If participants' hair was long enough, one sample of six cm hair (from the scalp) was taken and subsequently divided into two subsamples of three cm length. The following compounds were assessed: cocaine, benzoylecgonine, ethylcocaine, norcocaine, amphetamine, methamphetamine, MDMA, MDEA, MDA, morphine, codeine, methadone EDDP (primary methadone metabolite), tramadol, and methylphenidate.

For our routine protocol for drugs of abuse analysis a three step washing procedure with water (2 minutes shaking, 15ml), acetone (2min., 10ml) and finally hexane (2min., 10ml) of hair was performed. Then the hair samples were dried at ambient temperatures, cut into small snippets and extracted in two steps, first with methanol (5ml, 16hours, ultrasonication) and a second step with 3 ml MeOH acidified with 50 µL hydrochloric acid 33 % (3 hours, ultrasonication). The extracts were dried and the residue reconstituted with 50 µL MeOH and 500 µL 0.2 mM ammonium formate (analytical grade) in water. As internal standards deuterated standards of the following compounds were used,

added as mixture of the following compounds: cocaine-d3, benzoylecgonine-d3, ethylcocaine-d3, morphine-d3, MAM-d3, codeine-d3, dihydrocodeine-d3, amphetamine-d6, methamphetamine-d9, MDMA-d5. MDEA-d6, MDA-d5, methadone-d9, EDDP-d3, methylphenidate-d9, tramadol-d3, oxycodone-d3, and ephedrine-d3. All deuterated standards were from ReseaChem (Burgdorf, Switzerland), the solvents for washing and extraction were of analysis grade and obtained from Merck (Darmstadt, Germany); LC-solvents were of HPLC grade and were obtained from Sigma Aldrich (Buchs, Switzerland).

The LC-MS/MS apparatus was an ABSciex QTrap 3200 (Analyst software Version 1.5, Turbo V ion source operated in the ESI mode, gas 1, nitrogen (50 psi); gas 2, nitrogen (60 psi); ion spray voltage, 3500V; ion source temperature, 450°C; curtain gas, nitrogen (20 psi) collision gas, medium), with a Shimadzu Prominence LC-system (Shimadzu CBM 20 A controller, two Shimadzu LC 20 AD pumps including a degasser, a Shimadzu SIL 20 AC autosampler and a Shimadzu CTO 20 AC column oven, Shimadzu, Duisburg, Germany). Gradient elution was performed on a separation column (Synergi 4µ POLAR-RP 80A, 150x2.0 with a POLAR-RP 4x2.0 Security Guard Cartridge, (Phenomenex, Aschaffenburg, Germany). The mobile phase consisted of 1mM ammonium formate buffer adjusted to pH 3,5 with formic acid (eluent A) and acetonitrile containing 1mM ammonium formate and 1 mM formic acid (eluent B). The Analysis was performed in MRM mode with two transitions per analyte and one transition for each deuterated internal standard, respectively.

sMethods 3: Construction of cognitive domain scores

Fifteen predefined main cognitive test parameters were z-transformed on the basis of means and standard deviations of the control group. Two cocaine users were missing either SWM or PAL parameters due to technical problems. These values were excluded from the domain computation. If necessary, test scores were reversed so that high scores always indicated a better cognitive performance. These parameters were reduced to the four the cognitive domains attention, working memory, declarative memory, and executive function according to theoretical a priori considerations and in accordance with previous literature findings as cited below. Furthermore, these four z-scored domains were equally integrated into a broad global cognitive index (GCI).

Attention. To assess attentional capacity, we focused primarily on sustained attention by including the two RVP parameters discrimination performance A' and total of hits (Jones et al., 1992). In order to diversify this domain we added the RAVLT test parameter trial 1, a supraspan measure with a large attentional component (Lezak et al., 2004).

Working Memory. The SWM parameter number of total errors tested the capability to retain spatial information and to manipulate remembered items in working memory (Morris et al., 1988). The LNST measured the verbal working memory by summing up the number of correct responses (Wechsler,

1997). The third parameter was the number of correctly located patterns after the first presentation, a PAL parameter measuring primarily a visual working memory component (Sahakian et al., 1988).

Declarative memory. The RAVLT was administered to assess the verbal declarative memory performance (Helmstaedter et al., 2001). Performance was measured by the parameters learning performance (∑trials 1-5), delayed recall (trial 7), and an adjusted recognition performance (p(A))(Helmstaedter et al., 2001). To capture the visual declarative memory, we used the two PAL parameters: adjusted total of errors and adjusted total of trials (Sahakian et al., 1988).

Executive Functions. Executive functions are commonly separated into the three components shifting, updating, and inhibition (Miyake et al., 2000). Since inhibition in CU is currently investigated in another study from our laboratory (Vonmoos et al., 2013b), we focused on shifting (IED) and updating tasks (SWM strategy, RAVLT recall consistency). The IED assessed visual discrimination, attentional set formation, maintenance, shifting, and flexibility (Downes et al., 1989). The considered test parameters were the total of errors and trials adjusted to the amount of completed stages. Hereby, we added the SWM strategy score assessing the applied heuristic strategies (Morris et al., 1988), and the RAVLT recall consistency, a parameter impaired in patients with prefrontal lesions (Alexander et al., 2003; Benedict et al., 2005; Jokeit et al., 1997) and related with measures of executive functions (Beebe et al., 2000).

2.7.2 Results

sTable 1. Intercorrelation cocaine use parameters in cocaine users

	1)	2)	3)	4)	5)	6)	7)	8)	9)	10)	11)	12)	13)
1) Cumulative dose (grams) log	1	*.24	*.22	***.57	.02	***.62	-.09	***.34	***.37	*.21*	***.39	***.36	***.81
2) Times per week		1	***.70	-.09	.09	.17	.15	.18	.14	*.23	.16	.18	**.32
3) Grams per week log			1	-.13	.04	.13	.13	.04	-.04	.18	-.01	.03	.19
4) Years of use				1	-.03	.06	-.10	***.42	***.37	***.37	***.39	***.42	***.56
5) Age of onset					1	.07	-.17	.16	.20	.05	.17	.17	.09
6) Maximum dose (grams/day)						1	-.09	.14	*.23	-.08	*.22	.16	***.72
7) CCQ sum score (0-70)							1	.03	-.01	-.03	.01	.02	-.12
8) Hair analysis Cocaine pg/mg								1	***.91	***.70	***.86	***1.00	***.59
9) Hair analysis Benzoylecgonine pg/mg									1	***.55	***.95	***.94	***.61
10) Hair analysis Cocaethylene pg/mg										1	***.62	***.68	***.33
11) Hair analysis Norcocaine pg/mg											1	***.89	***.60
12) Hair analysis $Cocaine_{total}$ pg/mg												1	***.61
13) Severity of cocaine use Index[a]													1

Analyses only for cocaine users (n=98; Hair samples were voluntary and are deficient for 1 recreational cocaine user). Pearson's product-moment correlation. Significant correlations (two-tailed) are marked: *p<.05; **p<.01; ***p<.001.
[a] Severity of cocaine use Index corresponds to the mean of the z-transformed parameters cumulative dose, grams per week, years of use, maximum dose, and hair analysis $Cocaine_{total}$.

sTable 2. Correlations between cognitive test scores and cocaine use parameters in cocaine users

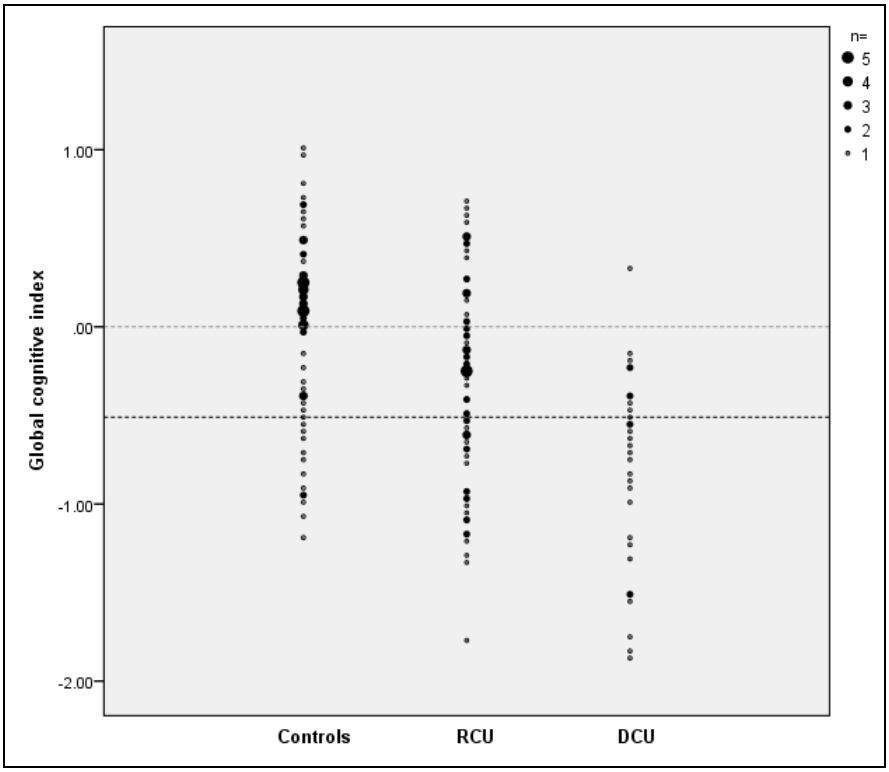
	Attention			Working memory			Declarative memory					Executive functions			
	RVP A'	RVP Hits	RAVLT Trial 1	LNST Score	SWM Error[d]	PAL First trial[d]	RAVLT ? Trials 1-5	RAVLT p(A)	RAVLT Trial 7	PAL Errors adj.[d]	PAL Trials adj.[d]	IED Errors adj.	IED Trials adj.	SWM Strat.[d]	RAVLT Recall cons.
Cumulative dose (grams) log[a]	*-.23	*-.22	***-.38	**-.30	***.33	*-.26	***-.43	**-.31	***-.34	**.29	**.29			*.24	***-.39
Cumulative dose (grams) log, adj. age[b]	**-.27	**-.26	***-.35	**-.27	**.27	*-.22	***-.39	**-.31	***-.35	*.25	*.22				***-.37
Times per week[a]							*-.20		-.17						*-.25
Grams per week log[a]															
Years of use[a]			*-.25	*-.21	**.32	*-.22	***-.33	*-.23	-.20	.17	.20			***.35	**-.31
Years of use, adj. age[b]			-.19		*.23		*-.25	*-.25	*-.20					*.24	**-.30
Maximum dose (grams/day)[a]	*-.21	*-.21		*-.20			*-.24	*-.23	*-.22	.18					-.18
CCQ sum score (0-70)[a]															
Hair analysis Cocaine pg/mg[a,c]			-.18		.19		*-.24		-.19					.19	
Hair analysis Benzoylecgonine pg/mg[a,c]			*-.24	*-.23	*.23		**-.31		*-.24	.19	*.22			*.22	
Hair analysis Cocaethylene pg/mg[a,c]					**.27									**.27	
Hair analysis Norcocaine pg/mg[a,c]			**-.27	*-.22	**.29		**-.31		*-.23	.17	*.20			*.21	
Hair analysis $Cocaine_{total}$ pg/mg[a,,c,e]			-.19		*.21		*-.26		*-.20					.20	
Severity of cocaine use Index[a,f]			**-.31	**-.26	*.26		**-.44	*-.25	**-.32	.20	*.21			*.25	**-.38

Analyses only for cocaine users (n=98). Correlations with a p-level below 10% are shown, while significant correlations are marked as follows: *p<.05; **p<.01; ***p<.001.
[a] Pearson's product-moment correlation. [b] Partial Correlation corrected for age.
[c] Hair samples were voluntary and are deficient for 1 recreational cocaine user.
[d] Two cocaine users were missing either SWM or PAL parameters due to technical problems.
[e] $Cocaine_{total}$ = Cocaine + Benzoylecgonine + Norcocaine.
[f] Severity of cocaine use Index corresponds to the mean of the z-transformed parameters cumulative dose, grams per week, years of use, maximum dose, and hair analysis $Cocaine_{total}$.

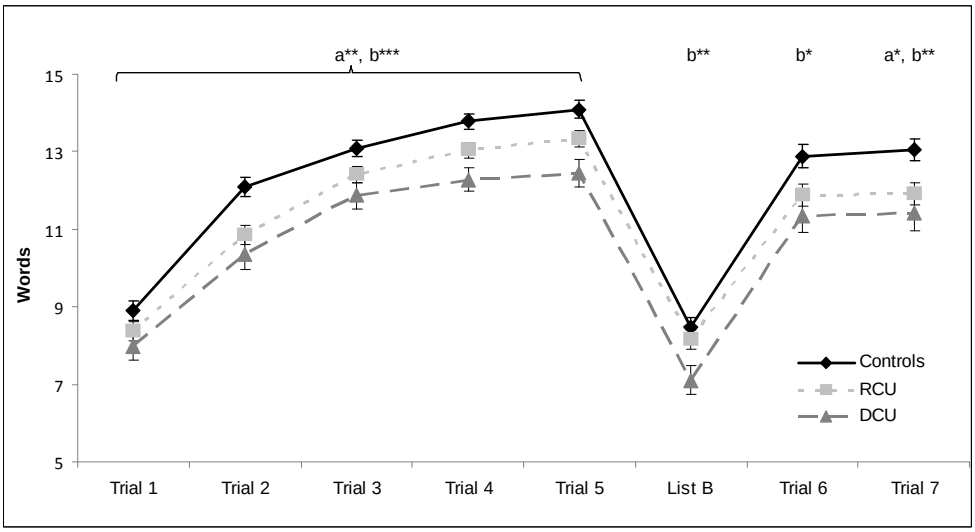
sTable 3. Predictors of the global cognitive index in cocaine users

	Model 1: Cumulative dose			Model 2: Years of use			Model 3: Weekly use		
	B	SE	β	B	SE	β	B	SE	β
Constant	.26	.33		-.10	.38		.53	.34	
Age	-.01	.01	-.16	.01	.02	.10	-.02	.01	**-.28
Depression	.00	.01	.04	.00	.01	.03	.00	.01	.02
ADHD	.00	.01	-.05	-.01	.01	-.11	-.01	.01	-.17
Craving for cocaine	-.01	.01	-.20	-.01	.01	-.15	-.01	.01	-.21
Urine sample (neg/pos)	.11	.14	.08	.08	.15	.05	.19	.14	.13
Cocaine cumulative dose (grams)	.00	.00	*-.29						
MDMA cumulative dose (tablets)	.00	.00	-.16						
Amphetamine cumulative dose (grams)	.00	.00	-.05						
Cannabis cumulative dose (grams)	.00	.00	-.08						
Cocaine years of use				-.04	.02	*-.29			
MDMA years of use				.00	.01	-.03			
Amphetamine years of use				.03	.02	.16			
Cannabis years of use				.00	.01	.05			
Alcohol years of use				.00	.02	-.01			
Nicotine years of use				-.02	.01	-.21			
Cocaine grams per week							.00	.01	-.02
MDMA tablets per week							-.15	.06	**-.25
Amphetamines grams per week							.11	.31	.03
Cannabis grams per week							-.01	.02	-.02
Alcohol grams per week							.00	.00	**.28
Cigarettes per week							.00	.00	*-.22
R^2			.22			.19			.29
F			**2.80			1.83			**3.20
p			.006			.06			.001

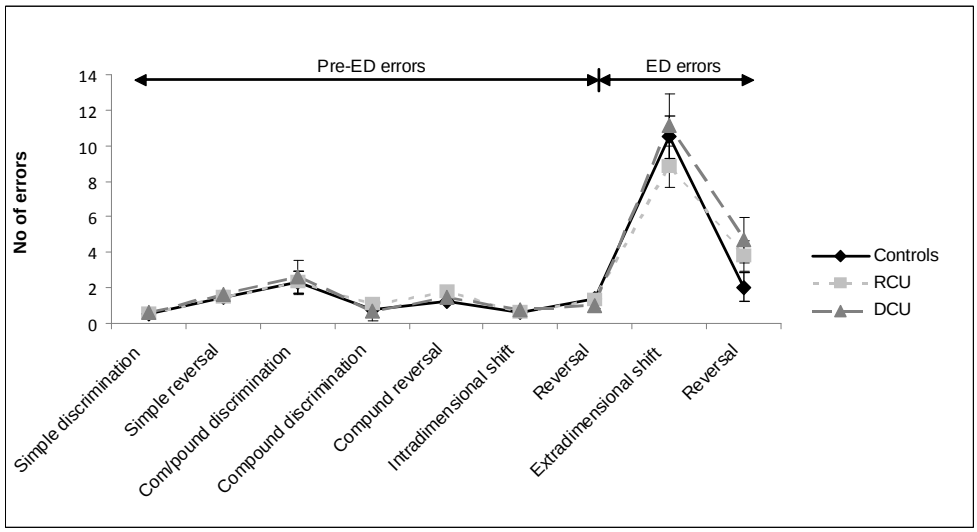
Multiple regression, only cocaine users (n= 98), *p<.05; **p<.01. Models included clinical variables linked to cognitive functioning (depression, ADHD, cocaine craving, and cocaine urine status) but included either cumulative, current, or duration of drug use parameters.
B, Unstandardized regression coefficient; SE, Unstandardized standard error; β, Standardized Beta.



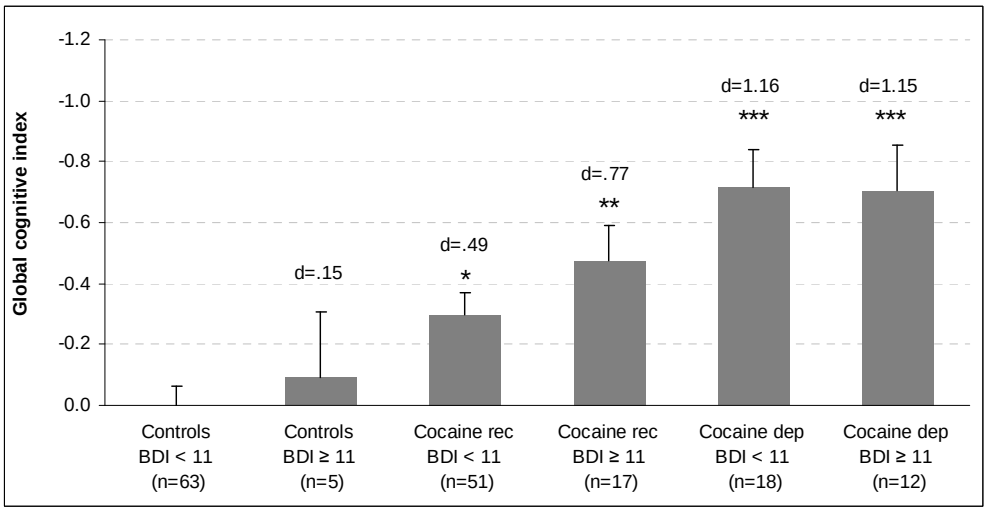
sFigure 1. GCI score scatterplot. Separated for control group (n=68), recreational cocaine user group (n=68), and dependent cocaine user group (n=30). The dotted black line represents the clinical criterion of -1 SD of the control group.



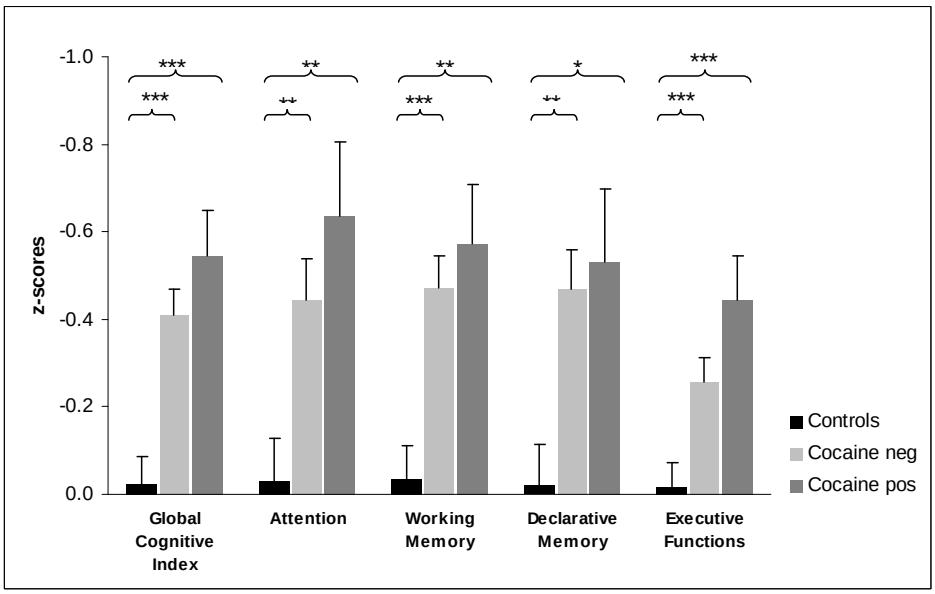
sFigure 2. RAVLT performance in the first five learning trials, the interference list B, the recall after interference trial 6, and the delayed recall trial 7 in the Ray Auditory Verbal Learning Test (RAVLT). Means and standard errors (corrected for age and verbal IQ). Separated for control group (n=68), recreational cocaine user group (n=68), and dependent cocaine user group (n=30). [a] Sidak post hoc tests: Controls vs. Cocaine rec. [b] Sidak post hoc tests: Controls vs. Cocaine dep. *p<.05, **p<.01, ***p<.001.



sFigure 3. IED performance. Error rates across the nine stages of the Intra/Extradimensional Attentional Set Shifting task (IED). Means and standard errors (corrected for age and verbal IQ). Separated for control group (n=68), recreational cocaine user group (n=68), and dependent cocaine user group (n=30). No significant pairwise Sidak post hoc tests.



sFigure 4. Impact depression status. Mean GCI scores and standard errors in groups stratified for cocaine use and BDI score. Values are corrected for age, verbal IQ, and cocaine gram/week. Group sizes (n) are shown. Significant Sidak post-hoc test vs. reference control group low depression (on the very left): *p<.05; **p<.01; ***p<.001. Cohen's d vs. control group low depression (on the very left).



sFigure 5. Impact current cocaine effects tested by urine status. Mean z-scores and standard errors for the global cognitive index and the four cognitive domains (values corrected for age and verbal IQ) in groups with controls (n=68), negative (n=75), and positive (n=22) urine samples. One hair sample (recreational cocaine user) was deficient. Sidak post-hoc tests: *p<.05; **p<.01; ***p<.001.

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3 Differences in self-reported and behavioral measures of impulsivity in recreational and dependent cocaine users

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Personal Contribution

MV collected, analyzed, and interpreted the data and wrote the manuscript. LMH, KHP, and DJ contributed to the data acquisition and/or revised the first draft of the manuscript. CS adjusted the SST. MRB conducted the hair analyses. BBQ designed the study, contributed to the data analysis, and revised the manuscript.

3.1 Abstract

Background. Dependent cocaine users consistently display increased trait impulsivity on self-report questionnaires and less consistently exhibit elevated motor impulsivity in some behavioral tasks. However, trait and behavioral impulsivity measures have rarely been investigated in recreational users. Therefore, we examined self-reported trait and motor impulsivities in recreational and dependent cocaine users to clarify the role of impulse control in cocaine addiction and non-dependent cocaine use.

Methods. We investigated relatively pure recreational (n=68) and dependent (n=30) cocaine users, as well as psychostimulant-naïve controls (n=68), with self-report questionnaires (Barratt Impulsiveness Scale 11; Temperament and Character Inventory) and behavioral tasks (Rapid Visual Information Processing Task; Stop-Signal Task).

Results. Compared with controls, recreational and dependent cocaine users displayed higher trait impulsivity and novelty seeking scores on self-report questionnaires. Trait impulsivity scores were strongly associated with an increased number of symptoms of depression and attention deficit hyperactivity disorder and correlated significantly with long-term cocaine intake parameters. By contrast, none of the behavioral motor impulsivity measures showed significant group effects or correlated with cocaine use parameters. The correlations among the self-report measures were high, but self-reports were scarcely correlated with behavioral task measures.

Conclusions. These findings suggest that relatively pure cocaine users already display increased trait impulsivity at a recreational level of use. However, the results do not indicate any cocaine-related elevation of behavioral impulsivity in terms of motor or response inhibition. In summary, our data imply that elevated trait impulsivity is not a specific feature of dependent cocaine use.

3.2 Introduction

According to the United Nations Office on Drugs and Crime (2012), the annual number of cocaine users (CU) is estimated to be up to 20 million people worldwide. Despite the high addictive potential of cocaine (Nutt et al., 2007), a substantial proportion of CU display a recreational and non-dependent pattern of use (European Monitoring Centre for Drugs and Drug Addiction, 2012).

For years, impulsivity has been recognized as a fundamental feature of substance users (de Wit, 2009). During the past two decades, a growing body of literature has consistently linked impulsivity to the use of cocaine and postulated impaired cognitive control in CU (Beveridge et al., 2008; Bolla et al., 2004; Garavan and Hester, 2007). This relationship has recently been investigated with not only behavioral techniques but also neurobiological and imaging techniques (Perry and Carroll, 2008). Because such imaging studies in chronic CU have repeatedly reported reductions in gray matter density in the dorsolateral prefrontal cortex, anterior cingulate cortex, and orbitofrontal cortex (Bolla et al., 2004; Ersche et al., 2011; Franklin et al., 2002; Matochik et al., 2003), evidence has accumulated that cocaine affects the very same brain regions that are crucially involved in cognitive control (Beveridge et al., 2008; Cabeza and Nyberg, 2000; Garavan and Hester, 2007) and, consequently, impulsivity (Dalley et al., 2011; Garavan and Hester, 2007).

Impulsivity, a construct with multiple facets (Evenden, 1999), is generally defined as behavior that occurs rapidly and lacks planning and foresight (Moeller et al., 2001a). Various instruments exist that measure a range of attitudes generally termed as “impulsive” (Dawe et al., 2004). Regarding substance use, previous studies primarily focused on constructs such as trait impulsivity, disinhibition, novelty seeking, and reward discounting (Dawe et al., 2004; de Wit, 2009). Whereas trait impulsivity was mainly assessed with self-report questionnaires relying on individual self-perception, impulsive action or choice was assessed with behavioral tasks (Winstanley et al., 2010). However, trait and behavioral impulsivity measures commonly displayed only slight correlations in healthy individuals (Lijffijt et al., 2004; Reynolds et al., 2006).

Chronic or dependent cocaine use has consistently been associated with higher scores for trait impulsivity and novelty seeking on self-report questionnaires. Research has also revealed that dependent cocaine users (DCU) display impaired performance in behavioral impulsivity measures such as Stop-Signal and Go/No-go tasks (Ersche et al., 2010; Perry and Carroll, 2008; Verdejo-Garcia et al., 2008). Preliminary data from a small study using the Stop-Signal Task (SST) have also suggested impaired inhibitory control in recreational cocaine users (RCU)(Colzato et al., 2007). Additionally, a large study has confirmed higher self-reported impulsivity in recreational stimulant users (Reske et al., 2010a).

Although the link between impulsivity and cocaine use seems to be proven, there exists a lack of clarification on the relation between different facets of impulsivity and the extent of cocaine use. It is also unknown whether elevated impulsivity affects only DCU or whether RCU are also affected.

Clarifying this issue is important notably with regard to risk markers, prevention, and treatment success (Patkar et al., 2004). Studies investigating impulsivity in a large sample of pure RCU, with little or no polydrug use, do not exist. Furthermore, impulsivity analysis studies categorized for groups of differing cocaine use patterns, ranging from RCU to DCU, have not been published thus far. Therefore, we investigated fairly large samples of relatively pure RCU, DCU, and matched stimulant-naïve healthy controls with a comprehensive battery of commonly used impulsivity measures (de Wit, 2009; Perry and Carroll, 2008). The aims were to examine different aspects of impulsivity and to clarify the role of impulsivity in cocaine addiction and controlled use. Based on previous results of elevated impulsivity scores in DCU, we expect to find increased trait and behavioral impulsivity in DCU and similar, albeit less pronounced, results in RCU. Because attention deficit hyperactivity disorder (ADHD)(Wilson, 2007), craving (Tziortzis et al., 2011), and depression (Swendsen and Merikangas, 2000) have been linked to both impulsivity and substance use, we also assessed their relationships with cocaine use. Finally, by performing quantitative urine and hair toxicology analyses, we were able to characterize objectively the participants' drug use over the past six months.

3.3 Method

3.3.1 Participants

The study included 68 RCU, 30 DCU, and 68 healthy and cocaine-naïve controls (recruitment and selection details **sMethods 1**). Specific inclusion criteria for the two user groups were cocaine as the primary used illegal drug, cocaine use of >0.5g per month, and abstinence duration of <6 months. Cocaine dependence was diagnosed in accordance with the *Diagnostic and Statistical Manual of Mental Disorders IV* (DSM-IV)(American Psychiatric Association, 1994), with only DCU fulfilling the dependence criteria. Exclusion criteria for all participants were an acute or previous neurological disorder or head injury, any clinically significant medical diseases, and use of prescription drugs affecting the brain. Additional exclusion criteria for the control subjects were any Axis I DSM-IV psychiatric disorder, including ADHD, and any form of addiction or regular illegal drug use (lifetime >15 occasions), with the exception of recreational cannabis use. Specific exclusion criteria for the CU groups were use of opioids, a polytoxic drug use pattern, and any Axis I DSM-IV adult psychiatric disorders – with the exception of cocaine, cannabis, and alcohol abuse; history of affective disorders (acute major depression was excluded); and ADHD. All participants were asked to abstain from illegal substances for a minimum of 72h and from alcohol for at least 24 h before the testing session. Compliance with these instructions was controlled by urine and 6-month hair toxicologies (**sMethods 2**). The study was approved by the Cantonal Ethics Committee of Zurich. All participants provided written informed consent and were compensated for their participation.

3.3.2 Procedure

The cross-sectional data presented in this article were collected as part of the longitudinal Zurich Cocaine Cognition Study ($ZuCo^2St$) (Hulka et al., 2013a; Preller et al., 2013b; Vonmoos et al., 2013a). The Structured Clinical Interview for DSM-IV Axis I (SCID-I) disorders was carried out by trained psychologists. The Mehrfachwahl Wortschatz Intelligenztest (MWT-B) was applied to estimate premorbid verbal intelligence (Lehrl, 1999). Drug use was assessed by means of a structured and standardized Interview for Psychotropic Drug Consumption (Quednow et al., 2004). The brief version of the Cocaine Craving Questionnaire (CCQ) was used to capture current cocaine craving (Sussner et al., 2006). The current severity of depression was measured by the Beck Depression Inventory (BDI)(Beck et al., 1961), and the ADHD self-rating scale (ADHD-SR)(Roesler et al., 2004) captured the DSM-IV criteria of ADHD. To consider the various aspects of impulsivity, we applied four measures often used in substance use studies (de Wit, 2009; Perry and Carroll, 2008): two self-report questionnaires for trait impulsivity (*Barratt Impulsiveness Scale, BIS-11*) (Patton et al., 1995) and novelty seeking (*Temperament and Character Inventory Novelty Seeking Scale, TCI NS*) (Cloninger et

al., 1999) as well as the two behavioral tasks, *Rapid Visual Processing* (*RVP*; www.cantab.com) and *SST* (Logan, 1994) for motor or response inhibition (details in **sMethods 3**). The RVP was based on a standardized procedure described in the test manual (www.cantab.com), and the SST was based on the stop-signal paradigm software STOP-IT (Verbruggen et al., 2008). The SST requires subjects to respond quickly to pseudo-randomly presented visual go-signals on a computer screen (arrows to left/right, 50% each) and to inhibit a response when an auditory stop-signal occurs (25% of trials). Thirty-two not further analyzed practice trials were followed by three blocks of 64 trials. A staircase tracking procedure systematically varied the time between the go stimuli and stop signals until the stop-signal delay was found (the point when the participant was able to inhibit the responses 50% of the time).

The behavioral tasks were always presented in the same order during a standard neuropsychological test battery, as published elsewhere (Vonmoos et al., 2013a). Participants were allowed to take breaks at any time, and smoking was permitted during the breaks.

3.3.3 Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics 19.0. Frequency data were analyzed by means of Pearson's chi-square test, and quantitative data by analysis of variance (ANOVA). Sidak post-hoc comparisons were performed based on significant main effects.

Because evidence suggests that some facets of impulsivity change throughout the life span (Steinberg et al., 2008), age was introduced as a covariate in analysis of covariance (ANCOVA; uncorrected ANOVA in **sTable 1**). Pearson's product-moment correlation analyses were conducted across a consolidated CU group to relate cocaine use parameters to each other and to impulsivity measures. Cumulative cocaine use and weekly use in grams were ln-transformed for statistical analyses because of the highly skewed distribution and the resulting deviation from the normal distribution (Shapiro-Wilk $W<.001$).

Some data were missing owing to incomplete questionnaires (TCI: 1 control, 2 DCU) or technical failures (RVP: 1 control; SST: 1 control, 1 RCU, 1 DCU; urine toxicology: 1 RCU; hair toxicology: 3 controls, 1 RCU).

For the SST parameter stop-signal reaction time (SSRT), reliable estimates, as calculated in this study, depend on a horse-race model with a staircase tracking procedure, resulting in a probability (respond/signal) of ideally .5 (Verbruggen et al., 2008). Because the SSRT analysis is not useful for subjects significantly differing from this value (Verbruggen et al., 2008), we excluded an additional 6 participants (2 controls, 2 RCU, 2 DCU) with a deviation of more than two standard deviations of the total sample.

Possible confounding factors (recent cocaine/cannabis use, age of onset, duration of cocaine use, cocaine binging, craving for cocaine, ADHD, and depression) were defined based on theoretical a

priori considerations (**sMethods 4**). To limit the data volume, we focused on the most common parameters of the four measures.

3.4 Results

3.4.1 Demographic characteristics and drug use

The groups were matched for age, sex distribution, smoking status, and verbal IQ (**Table 1**). However, DCU had fewer years of education than controls and RCU. As expected, all three groups differed significantly in BDI and ADHD-SR scores, with DCU scoring highest and controls scoring lowest.

Table 1. Demographic Data

	Controls	RCU	DCU	$F/\chi^2/T^a$	df, df_{err}	p
N	68 (41%)	68 (41%)	30 (18%)			
Age (y)	30.3 (9.2)	28.7 (6.2)	32.5 (9.0)	2.39[a]	2, 163	.10
Sex (f/m)	21 / 47	18 / 50	8 / 22	0.38[b]	2	.83
Verbal IQ (MWT-B)	104.4 (9.7)	103.2 (9.6)	99.7 (9.1)	2.46[a]	2, 163	.09
School education (y)	10.7 (1.8)	10.5 (2.0)	9.5 (1.2)**°	4.82 [a]	2, 163	**.01**
Smoking / Non-smoking[d]	53 / 15	53 / 15	24 / 6	0.06[b]	2	.97
ADHD-SR sum score (0-22)	7.6 (4.8)	13.2 (9.0)***	17.1 (8.7)***°	19.52 [a]	2, 163	**<.001**
ADHD DSM IV (y/n)[e]	0 / 68	14 / 54	8 / 22	18.27[b]	2	**<.001**
BDI sum score (0-63)	4.6 (4.4)	7.4 (6.1)*	11.8 (8.6)***°°	15.01 [a]	2, 163	**<.001**
BDI depression status (y/n)[f]	5 / 63	17 / 51	12 / 18	15.07[b]	2	**<.001**
Craving for cocaine (0-70)	-	19.0 (9.1)	20.3 (11.4)	0.60[c]	1, 96	.55

Means and standard deviations. Significant p values are shown in bold. Sex, smoking, BDI depression status, and ADHD-SR DSM-IV are shown in frequency data.
[a] ANOVA F-test (all groups), [b] χ^2 test (all groups) for frequency data, or [c] independent T-test (cocaine users only).
[d] Smoking habits were assessed by the Fagerstroem Test of Nicotine Dependence (Heatherton et al., 1991).
[e] ADHD-SR, ADHD self rating scale (cut-off DSM-IV criteria).
[f] BDI, Beck Depression Inventory (cut-off ≥11).
[*] Significant Sidak post-hoc test vs. control group: *p<.05; **p<.01; ***p<.001.
° Significant Sidak post-hoc test vs. RCU group: °p<.05; °°p<.01.

Hair samples revealed a clear dominance of cocaine compared with other illegal drugs, as set out by the inclusion criteria (**Table 2**). Notably, hair concentrations of cocaine and its metabolites were highly correlated with self-reported cumulative dose and duration of use (**sTable 2**). Although the RCU were regular CU, with a mean weekly consumption of about 1g of cocaine, they did not fulfill the DSM-IV criteria for dependence. Some participants tested positive for cocaine and cannabis in urine screening; instead of excluding these participants, we decided to investigate the acute and post-acute effects of the drugs on these participants.

Table 2. Pattern and amount of drug use

	Controls (n=68)	RCU (n=68)	DCU (n=30)
Cocaine			
Times per week[a]	-	1.1 (1.0)	2.9 (2.6)
Grams per week[a]	-	1.1 (1.4)	7.9 (15.8)
Years of use	-	6.5 (4.0)	9.4 (6.5)
Maximum dose (grams/day)	-	3.5 (2.5)	9.4 (8.4)
Cumulative dose (grams)	-	519.7 (751.2)	5500.9 (9635.2)
Last consumption (days)[b]	-	27.5 (37.6)	21.0 (33.6)
Hair analysis $Cocaine_{total}$ pg/mg[c,e]	-	3347 (5580)	27798 (40226)
Hair analysis Cocaine pg/mg[c]	-	2739 (4628)	22164 (32609)
Hair analysis Benzoylecgonine pg/mg[c]	-	546 (919)	5048 (7711)
Hair analysis Cocaethylene pg/mg[c]	-	276 (316.)	2006 (3656)
Hair analysis Norcocaine pg/mg[c]	-	62 (101)	586 (758)
Urine toxicology (neg/pos)[d]	68 / 0	57 / 10	18 / 12
Alcohol			
Grams per week[a]	116.8 (122.6)	167.8 (117.5)	188.5 (260.6)
Years of use	13.2 (9.3)	11.2 (5.1)	13.5 (9.5)
Nicotine			
Cigarettes per day[a]	9.3 (9.5)	11.7 (8.8)	15.7 (13.5)
Years of use	9.2 (9.2)	9.6 (6.4)	14.2 (9.3)
Cannabis			
Grams per week[a]	0.5 (1.0)	0.9 (2.1)	1.2 (3.7)
Years of use	4.7 (6.5)	7.7 (6.0)	10.5 (9.9)
Cumulative dose (grams)	358.3 (846.2)	1042.8 (1780.0)	3550.3 (5959.0)
Last consumption (days)[b]	36.2 (50.1); n=33	22.1 (32.3); n=44	25.7 (32.8); n=20
Urine toxicology (neg/pos)[d]	58 / 10	55 / 12	20 / 10
Amphetamine			
Grams per week[a]	0.0 (0.0)	0.1 (0.2)	0.0 (0.2)
Years of use	0.0 (0.1)	1.6 (3.0)	1.5 (3.2)
Cumulative dose (grams)	0.2 (1.4)	21.2 (56.8)	22.3 (62.8)
Last consumption (days)[b]	121.6 (0.0), n=1	61.8 (51.3); n=25	78.4 (75.4); n=6
Hair analysis Amphetamine pg/mg[c]	1 (7)	76 (257)	60 (169)
MDMA			
Tablets per week[a]	-	0.1 (0.3)	0.4 (1.8)
Years of use	0.3 (1.7)	2.5 (3.8)	3.1 (5.2)
Cumulative dose (tablets)	0.9 (2.9)	35.9 (90.5)	157.4 (393.5)
Last consumption (days)[b]	-	75.1 (84.8); n=20	82.1 (45.4); n=9
Hair analysis MDMA pg/mg[c]	3 (16)	545 (1598)	255 (653)
Hallucinogens			
Cumulative dose (times)	0.9 (2.2)	6.0 (14.6)	6.9 (11.8)

Means and standard deviations. Use frequency, duration of use, and cumulative doses are averaged within the total group.
[a] Average use during the last 6 months.
[b] Last consumption is averaged only for persons who used the drug in the last 6 months. In this case, sample size (n) is shown.
[c] Cut-off values for cocaine = 500 pg/mg and for amphetamines/MDMA = 200 pg/mg (Cooper et al., 2012).
[d] Cut-off values for cocaine = 150 ng/ml and for Tetrahydrocannabinol 50 ng/ml (Substance Abuse and Mental Health Services Administration, 2008).
[e] $Cocaine_{total}$ (= Cocaine + Benzoylecgonine + Norcocaine) is a more robust procedure for discrimination between incorporation and contamination of hairs (Hoelzle et al., 2008).

3.4.2 Impulsivity measures

BIS-11. RCU and, to an even greater extent, DCU exhibited elevated trait impulsivity, as measured by the BIS-11 total score (linear trend: p_{trend}<.001) (**Table 3**, **Figure 1**), compared with controls. Similarly, all three subscales showed significant main group effects (p_{trend}<.01). In particular, attentional impulsiveness differed significantly among all three groups, whereas motor and non-planning impulsiveness showed substantial increments in both user groups but did not differentiate between them. Correlation analyses within the consolidated group of CU indicated an association between all BIS-11 scales and the two long-term cocaine use parameters of cumulative dose and duration of cocaine use (**Table 4**), as well as the number of ADHD and depression symptoms (**Table 5**). Furthermore, attentional impulsiveness correlated strongly with craving for cocaine (**Table 4**).

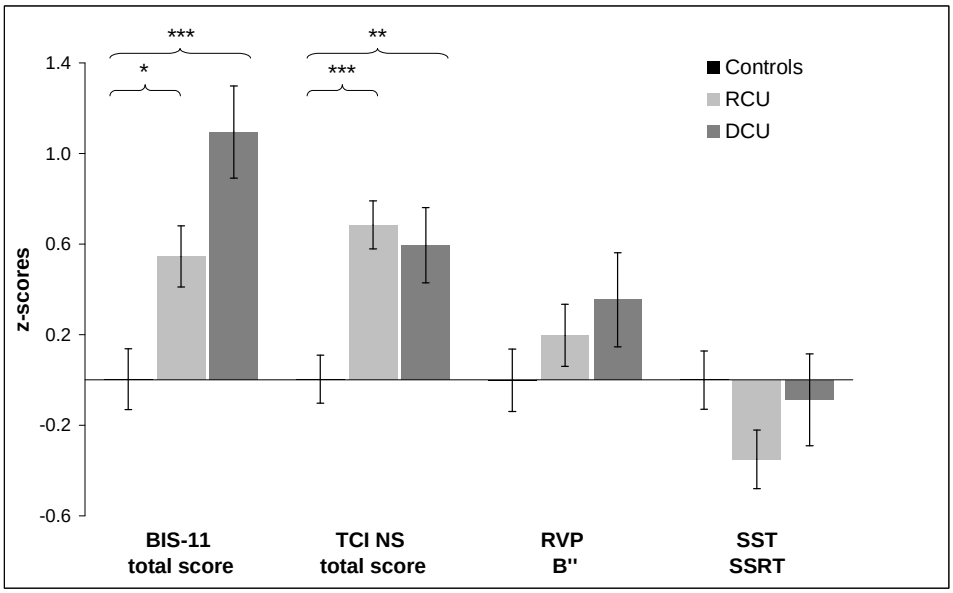

Figure 1. Comparison of z-standardized impulsivity measures in recreational (RCU) and dependent (DCU) cocaine users as well as controls. Mean z-scores and standard errors (corrected for age). The main parameters of the four measures were z-transformed based on means and standard deviations of the control group. If necessary, test scores were reversed so that higher bars always indicated higher trait impulsivity (BIS-11) / novelty seeking (TCI NS) / motor impulsivity (RVP, SST). Sidak post-hoc tests: *p<.05; **p<.01; ***p<.001.

TCI NS. Both CU groups showed substantially higher scores than controls in the NS total score, as well as in the sub-scores for extravagance, disorderliness, and, to a lesser degree, impulsiveness. RCU did not significantly differ from DCU for any of these scores (**Table 3**, **Figure 1**). The exploratory excitability scores were quite similar for all three groups, but they negatively correlated with the cocaine metabolites, benzoylecgonine and norcocaine, in the hair samples (**Table 4**).

Table 3. Impulsivity measures

Measure	n[a]	Controls	RCU	DCU	F	df, df_{err}	p	p, Sidak post-hoc: Controls vs. RCU	p, Sidak post-hoc: Controls vs. DCU	p, Sidak post-hoc: RCU vs. DCU	Cohen's d: Controls vs. RCU	Cohen's d: Controls vs. DCU	Cohen's d: RCU vs. DCU
Barratt Impulsiveness Scale (BIS-11)													
FI Attentional Impulsiveness	68/68/30	14.7 (0.4)	16.3 (0.4)	18.7 (0.7)	12.982	2, 162	**<.001**	**.03**	**<.001**	**.01**	.42	1.04	.62
FII Motor Impulsiveness	68/68/30	22.5 (0.5)	24.3 (0.6)	25.9 (0.8)	6.435	2, 162	**.002**	.06	**.003**	.33	.39	.73	.33
FIII Nonplanning Impulsivenes	68/68/30	26.3 (0.5)	27.9 (0.5)	29.1 (0.8)	4.570	2, 162	**.01**	.11	**.02**	.56	.35	.61	.26
Bis-11 Total score	68/68/30	63.4 (1.3)	68.5 (1.3)	73.6 (1.9)	10.803	2, 162	**<.001**	**.02**	**<.001**	.08	.46	.93	.47
Temperament and Character Inventory													
NS1 Exploratory excitability	67/68/28	7.5 (0.3)	8.0 (0.3)	7.2 (0.4)	1.904	2, 159	.15	.34	.92	.24	.26	.13	.39
NS2 Impulsiveness	67/68/28	4.8 (0.3)	5.9 (0.3)	6.0 (0.5)	4.258	2, 159	**.02**	**.03**	.09	1.00	.44	.48	.04
NS3 Extravagance	67/68/28	5.8 (0.2)	7.1 (0.2)	7.4 (0.4)	9.486	2, 159	**<.001**	**<.001**	**.002**	.89	.61	.75	.14
NS4 Disorderliness	67/68/28	4.4 (0.2)	5.8 (0.2)	5.7 (0.4)	10.348	2, 159	**<.001**	**<.001**	**.008**	1.00	.68	.64	.04
Novelty seeking Total score	67/68/28	22.5 (0.7)	26.8 (0.7)	26.3 (1.1)	11.384	2, 159	**<.001**	**<.001**	**.009**	.96	.73	.64	.10
Rapid Visual Processing Task													
Response bias B'	67/68/30	.949 (0.0)	.937 (0.0)	.928 (0.0)	1.160	2, 161	.32	.67	.39	.90	.18	.32	.14
Mean latency (ms)	67/68/30	404.7 (11.0)	418.3 (11.0)	416.2 (16.6)	.421	2, 161	.66	.76	.92	1.00	.15	.13	.02
Total false alarms	67/68/30	1.3 (0.2)	1.9 (0.2)	2.1 (0.4)	2.850	2, 161	.06	.19	.11	.89	.32	.46	.14
Impulsivity-score	67/68/30	.00 (0.2)	.23 (0.2)	.44 (0.3)	1.114	2, 161	.33	.70	.40	.88	.17	.31	.15
Stop-Signal Task													
p(correct inhibition)[b]	67/67/29	54.8 (1.4)	54.7 (1.4)	50.4 (2.1)									
RT on go trials (ms)[c]	67/67/29	765.2 (23.2)	728.7 (23.3)	734.4 (35.6)	.671	2, 159	.51	.61	.85	1.00	.19	.16	.03
p(correct responses on go trials)[b]	67/67/29	94.4 (1.4)	90.9 (1.4)	94.0 (2.1)	1.759	2, 159	.18	.21	1.00	.53	.31	.03	.28
RT on signal-respond trials (ms)[c]	67/67/29	672.9 (21.6)	651.1 (21.7)	647.1 (33.2)	.339	2, 159	.71	.86	.89	1.00	.12	.14	.02
Stop-signal reaction time, SSRT (ms)	65/65/27	298.1 (7.8)	277.1 (7.8)	292.9 (12.1)	1.885	2, 153	.16	.17	.98	.62	.33	.08	.25

Means and standard errors. ANCOVA (all groups, corrected for age). Significant p values are shown in bold.
The robustness of these parametric tests was confirmed using bootstrap simulations with 1000 replications. Thereby, no pairwise Sidak post-hoc comparison above turned from a significant group difference into a non-significant.
[a] Sample size control group/RCU/DCU. For details see *Statistical analysis*.
[b] p( ) = Percentage.
[c] RT = Reaction time.

RVP. The response bias B" and a calculated impulsivity-score (=$z_{false\ alarms} - z_{latency}$, **sMethods 3**) revealed gradual group differences, but neither a main group effect nor significant linear trends (B": p_{trend}=.15; impulsivity-score: p_{trend}=.16) occurred (**Table 3**, **Figure 1**). Similarly, no substantial effects were found for mean latency. Total false alarms featured a linear trend (p_{trend}< .05) and a substantial main group effect, but they were missing significant Sidak comparisons. None of these indicators showed a significant correlation with cocaine use parameters (**Table 4**).

SST. None of the SST parameters revealed a significant main group effect. For the main parameter SSRT, the results did not change (**Table 3**, **Figure 1**, **sFigure 1**) when we again included the 6 participants (2 controls, 2 RCU, 2 DCU) with more than two standard deviations of the total sample (F(2,159)=2.07, p=.13); when we excluded all participants (8,10,2) with an SST software-based exclusion criterion of p=.0, which determined all subjects with an inhibition rate of significantly more or less than 50% (Verbruggen et al., 2008) (F(2,133)=1.08, p=.34); or when we focused only on CU with negative (65,55,16; F(2,132)=1.73, p=.18) or positive (65,10,11; F(2,82)=1.17, p=.32) urine samples for cocaine. Furthermore, none of these SST parameters did substantially correlate with a cocaine use parameter (**Table 4**).

Table 4. Correlations between cocaine use parameters, ADHD, BDI, and impulsivity measures in cocaine users

	BIS-11				TCI NS					RVP				SST						
	FI	FII	FIII	Total score	NS1	NS2	NS3	NS4	Total score	B"	M. Lat.	Total FA	Imp.-score	p[c] (corr. inhib)	RT[d] go trials	p[c] (corr. resp)	RT[d] s-r trials	SSRT	ADHD[e]	Depr.[f]
Times per week[a]	.19				-.18			-.19	-.19											
Grams per week log[a]					-.05			*-.21												
Years of use[a]	*.24	*.24	*.25	**.29															*.21	.19
Years of use, adj. for age[b]	**.30	**.30	**.33	***.37		.17													*.24	*.22
Age of onset[a]	-.18	-.19	*-.22	*-.24													.19			
Cumulative dose (grams) log[a]	**.27	**.28	*.23	**.31	-.18		.20												**.28	***.33
Cumulative dose (grams) log, adj. for age[b]	**.28	**.30	*.25	***.33	-.19														**.29	***.35
Maximum dose (grams/day)[a]					-.18														**.26	**.27
CCQ sum score (0-70)[a]	***.33			*.22	-.19							.19					*-.22		**.29	***.33
Hair analysis $Cocaine_{total}$ pg/mg[a]					*-.25															
Hair analysis Cocaine pg/mg[a]					*-.23															
Hair analysis Benzoylecgonine pg/mg[a]					**-.32													.19		
Hair analysis Cocaethylene pg/mg[a]																				
Hair analysis Norcocaine pg/mg[a]					*-.26*				-.18											

Correlations with a p-level below 10% are shown, while significant correlations are marked: *p<.05; **p<.01; ***p<.001.
[a] Pearson's product-moment correlation.
[b] Partial Correlation corrected for age.
[c] p( ) = Percentage.
[d] RT = Reaction time.
[e] ADHD as measured by number of ADHD symptoms in ADHD-SR.
[f] Depression as measured by BDI score.

3.4.3 Correlation analysis

The two self-report measures of BIS-11 und TCI NS were – with the exception of the TCI subscale, exploratory excitability – all positively correlated (**Table 5**). By contrast, none of the correlations between the two behavioral tasks was significant. Of the 81 correlations between self-report and behavioral impulsivity measures, only 2 correlations fell below a significance level of p<.01 (BIS-11 non-planning impulsiveness and SST p(correct inhibition); TCI disorderliness and SST RT on go trials).

Table 5. Correlation matrix for impulsivity measures, ADHD, and BDI in cocaine users

	2)	3)	4)	5)	6)	7)	8)	9)	10)	11)	12)	13)	14)	15)	16)	17)	18)	19)	20)
1) BIS-11 FI Attentional Imp.	***.51	***.43	***.75		**.23	.14	**.24	*.19										***.75	***.50
2) BIS-11 FII Motor Imp.	1	***.66	***.88		***.50	***.32	***.37	***.49	*-.20		*.18	*.16	-.13					***.47	***.31
3) BIS-11 FIII Nonplanning Imp.		1	***.85		***.51	***.40	***.41	***.47					**-.21	*-.19		*-.16		***.36	***.27
4) BIS-11 Total score			1		***.51	***.35	***.41	***.47	-.15		.13		*-.18	-.13				***.61	***.42
5) TCI NS1 Exploratory excitability				1	**.21	*.16	.13	***.57									*-.16		***-.37
6) TCI NS2 Impulsiveness					1	***.34	***.35	***.74	-.15		.14	*.19						*.16	
7) TCI NS3 Extravagance						1	***.42	***.70										.13	
8) TCI NS4 Disorderliness							1	***.69						**-.22		*-.18		***.28	
9) TCI Novelty seeking Total score								1				*.16		-.15				*.17	
10) RVP Response bias B"									1	**-.23	***-.96	***-.69					.14		
11) RVP Mean latency										1	***.27	***-.51							
12) RVP Total false alarms											1	***.69							
13) RVP Impulsivity-score												1							
14) SST p(correct inhibition)[c]													1	***.63	***-.32	***.56	***-.40		
15) SST RT on go trials[d]														1	***-.51	***.95	**-.25		
16) SST p(correct resp. on go trials)[c]															1	***-.54	***.52		
17) SST RT on signal-respond trials[d]																1	***-.32		
18) SST Stop-signal reaction time																	1		
19) ADHD[a]																		1	***.56
20) Depression[b]																			1

Pearson's product-moment correlation. Correlations with a p-level below 10% are shown, while significant correlations are marked: *p<.05; **p<.01; ***p<.001.
[a] ADHD as measured by number of ADHD symptoms in ADHD-SR.
[b] Depression as measured by BDI score.
[c] p( ) = Percentage.
[d] RT = Reaction time.

3.4.4 Cofactor analyses

ANCOVAs with controls and CU subgroups stratified for either cocaine or cannabis urine toxicology status (pos/neg), age of onset (>18/≤18 years), duration of cocaine use (≤10/>11 years), binge use (low/high), craving (low/high), ADHD (with/without), or depression (low/≥mild) (group assignments **sMethods 4**) revealed significant main group effects in the BIS-11 and TCI NS total scores for all eight cofactors (**sTable 3**). These effects are primarily based on substantial differences between controls and both CU subgroups. In-depth analysis of the factor duration of cocaine use suggested that trait impulsivity measured with the BIS-11 was more pronounced in long-term users (>10 years), a link that already became apparent in the significant correlations of the BIS-11 scores with years of cocaine use. Moreover, early age of onset was associated with slightly elevated BIS-11 total scores, again confirming the significant correlation of both parameters (**Table 4**). In line with recent studies (Crunelle et al., 2012; Ekinci et al., 2011; Nandagopal et al., 2011), the presence of ADHD or mild depression (BDI≥11) was associated with substantially higher BIS-11 total scores. For the two behavioral measures, RVP B" and SSRT, no main group effects were found.

3.5 Discussion

The aims of the present study were to examine trait and behavioral impulsivities in RCU and DCU and to clarify the role of impulsivity in cocaine addiction in contrast to controlled recreational use. The performance of hair toxicologies and comprehensive psychiatric diagnostics allowed the investigation of relatively pure cocaine users with little psychiatric comorbidity. As expected, CU displayed higher trait impulsivity and novelty seeking on self-report questionnaires (BIS-11, TCI) than controls; however, with the exception of the BIS-11 subscale attentional impulsiveness, RCU did not differ from DCU. Thus, elevated trait impulsivity is not an exclusive feature of addicted CU. Furthermore, more pronounced trait impulsivity was associated with an increased number of ADHD and depression symptoms in CU and with longer duration of cocaine use and higher cumulative dose. By contrast, none of the behavioral motor impulsivity measures (RVP, SST) showed significant group effects or correlated with any cocaine use parameter. Moreover, correlations among the self-report impulsivity measures were high, but none of the intercorrelations between behavioral task parameters was significant. In addition, we found that self-reports correlated only slightly with behavioral measures. This finding confirms those of previous studies with healthy controls (Lijffijt et al., 2004; Reynolds et al., 2006) and substance users (Clark et al., 2006; Ersche et al., 2011) that also reported no or only weak correlations between trait and behavioral impulsivity measures. Therefore, our results support the assumption that impulsivity is a multidimensional construct and that, to date, no comprehensive model exists that integrates all these seemingly important features of impulsivity (Perry and Carroll, 2008).

We found elevated trait impulsivity for RCU and, to an even greater extent, for DCU, thus confirming previous reports of higher BIS-11 scores for DCU compared with healthy controls (Ersche et al., 2011; 2010; Moeller et al., 2002). Similarly, the only recently published report that included RCU described enhanced BIS-11 total scores for 155 recreational prescription stimulant users but featured no separate analysis for the subgroup of 43 RCU (Reske et al., 2010a).

Together with the correlations between BIS-11 scores and several cocaine use parameters detected in the present study, these findings indicate a robust relationship between self-reported trait impulsivity and cocaine use. However, in our cross-sectional design, we cannot determine whether these impulsivity traits were preexistent, drug-induced, or both. Our results also revealed ADHD and depression to be important factors with regard to trait impulsivity in CU. These findings are in line with the frequent comorbidity of ADHD and depression with substance use disorders (Swendsen and Merikangas, 2000; van Emmerik-van Oortmerssen et al., 2012), with which they share some fundamental features: Whereas ADHD is characterized by inattentive and impulsive behavior (Wilson, 2007), there is evidence supporting a relationship between trait impulsivity and depression, especially as the BIS-11 total score is related to hopelessness and depression (Swann et al., 2008). Moreover, our

results confirm that of a recent small study in which ADHD in CU was associated with strongly increased trait impulsivity, as measured with the BIS-11 (Crunelle et al., 2012). By contrast, we found that craving for cocaine seemed to be only marginally associated with the BIS-11 total score, a finding that is in line with earlier studies (Moeller et al., 2001b; Tziortzis et al., 2011). Unlike in previous studies investigating alcohol binge drinking (Moreno et al., 2012) and binge eating (Waxman, 2009), we found that a cocaine binge profile was not associated with more pronounced trait impulsivity.

Novelty seeking, as measured by the Tridimensional Personality Questionnaire or its successor TCI, has repeatedly been linked to substance use (Lukasiewicz et al., 2008; Prisciandaro et al., 2012; Sher et al., 2000). A study focusing on stimulant-dependent individuals (with 93% DCU) found that these drug users reported higher sensation-seeking behavior than controls (Ersche et al., 2010), which is in line with the present findings indicating enhanced novelty seeking in CU in general but no substantial differences between RCU and DCU. Thus, increased novelty seeking does not seem to be decisive for the amount or pattern of cocaine use. Notably, a recent study found no difference between controls and DCU in the sensation-seeking subscale of the UPPS-P impulsive behavior scale (Albein-Urios et al., 2012). However, this subscale consisted of only 12 items and included two aspects of novelty seeking (tendency for exciting activities and openness for new experiences), whereas the TCI NS scale also tested for impulsiveness. Because we did not find any group differences in our TCI subscale of exploratory excitability, capturing similar aspects as the UPPS-P sensation seeking score (Cloninger et al., 1999), it might be concluded that impulsive rather than explorative aspects of novelty seeking are associated with repeated cocaine use.

None of the four RVP parameters proposed as impulsivity measures (Ersche et al., 2011) displayed significant group differences between CU groups and the control group. Thus, we replicated a recent study reporting no significant differences between controls and DCU for the RVP parameters B", total false alarms, and mean latency (Ersche et al., 2011). Previous research involving the RVP, which is typically used for measuring sustained attention, has revealed that the standard parameters for sustained attention (A', total hits) showed clear group differences between DCU and controls in both samples (Ersche et al., 2011; Vonmoos et al., 2013a). Only a single study has used the RVP to investigate impulsivity in RCU, albeit in a small sample size of 17 RCU and 24 controls (Soar et al., 2012). These authors reported a delayed mean latency in recreational users (p = .03), a finding that also does not support elevated behavioral impulsivity in RCU. However, it should be noted that the total number of false alarms was included in three of four RVP measures, and the false alarm rate was relatively low in all three groups. Consistent with previous findings, we thus confirm that these RVP parameters are not suitable in distinguishing impulsive behavior between controls and CU.

Previous studies in which the SST was applied to CU mostly found that CU showed decreased motor response inhibition, as measured by the main parameter SSRT (Verdejo-Garcia et al., 2008). Given that we found neither group differences nor any association with cocaine use patterns or parameters regarding the SSRT, we were unable to confirm these previous results. A previous study suggested that the abstinent duration in CU might play a role in motor impulsivity tasks (Li et al., 2010). In our study, CU reported a relatively long mean abstinence duration of ~25 days. A study that included DCU with a comparable abstinence period of at least 2 weeks showed slightly increased SSRT in these users (p <.05; d≈.65), but this difference was eliminated by adjustment for the post-signal slowing effect (Li et al., 2006). Other studies that included RCU (Colzato et al., 2007; Fillmore and Rush, 2002) or DCU (Ersche et al., 2011; 2012b) found significant group differences between CU and controls in SSRT showing moderate effect sizes. The main difference between these studies and ours is that CU either had recently used cocaine (Ersche et al., 2011; 2012b; Fillmore and Rush, 2002) or reported an abstinence duration of at least 2 days, which was not further verified (Colzato et al., 2007). Because our separate comparisons of CU with positive (n=21) or negative (n=71) urine samples did not show any group differences, we, however, cannot replicate these results either. Regarding the reaction time on go-signal, our data did not show significant group differences, a finding in line with those of previous studies investigating RCU (Colzato et al., 2007; Fillmore and Rush, 2002) or DCU (Li et al., 2006).

In summary, our SST results are largely similar to previous findings. However, with regard to the SSRT, none of our calculations with different sample compositions (ADHD, positive urine toxicology, etc.) could confirm an association with cocaine use. In this sense, we agree with Ersche et al. (2012) that impaired inhibitory control might not result from long-term drug use, but, in contrast to these authors, we also cannot conclude that deficient inhibitory motor control – as measured with the SSRT – is a familial trait of CU.

Given that the SSRT performance can be influenced by many factors, other possible reasons for conflicting results exist:

i) In most previous studies, different SST designs were applied, including different stimuli or signals, interval steps, numbers of blocks and trials, and probabilities of go trials. Accordingly, not all SST designs might have the same sensitivity in detecting group differences. We used an SST design consisting of three blocks of 64 trials, which might be less sensitive than SST designs with five blocks of 64 (Ersche et al., 2012b) or 104 trials (Colzato et al., 2007).

ii) The absolute SSRT values in the present study and those of two previous studies using a similar but extended SST design with five blocks of 64 trials are comparable. Our study found that RCU and DCU had SSRT values between 277ms and 293ms, and the DCU in the two previous studies had mean SSRT values of 263ms and 281ms (Ersche et al., 2011; 2012b). Whereas our controls revealed a mean SSRT of 298ms, controls from these previous studies displayed much lower SSRTs (235ms/239ms).

Therefore, the conflicting results of the present study versus those of (Ersche et al., 2011; 2012b) arise from differences between the control groups, not between the CU groups.
iii) Our sample is so far the first to comprise relatively pure CU, as confirmed by hair toxicologies. Therefore, it is possible that previous studies, non of which have applied hair toxicologies, measured the effect of polytoxic drug use, not pure cocaine use. Because subjects addicted to multiple substances have shown higher impulsivity scores on self-report questionnaires than subjects addicted to only one substance (McCown, 1988; O'Boyle and Barratt, 1993), it is reasonable to compare motor impulsivity in pure CU with that of CU with polysubstance use in future research.
iv) Impulsivity is associated not only with substance use disorders but also with several personality disorders, bipolar disorder, and ADHD (Moeller et al., 2001a; Wilson, 2007). Because the co-occurrence of cocaine dependence and personality disorders is associated with enhanced impulsivity (Albein-Urios et al., submitted), we tried to exclude subjects with severe psychiatric disorders or to analyze systematically their interaction with impulsivity. However, differences in the presence of comorbidities related to impulsive behavior between study samples might be another explanation for the conflicting SSRT results.
v) Several methods of estimating SSRT exist (Logan, 1994). One of them, the subtraction method (used in this study), is not suitable for subjects who inhibit significantly more or less than 50% of the trials. This situation can be handled either by excluding these subjects or by calculating the SSRT with another method (Verbruggen et al., 2008). Because the significance level of deviance can be interpreted in multiple ways, as well as the fact that not all studies applying SSRT exclude participants failing to fit the horse-race model or declare the exact estimation method, we cannot rule out that the SSRT calculation itself implies a fundamental data bias in previous studies.

This study has the following limitations: i) Because the DSM-IV criteria for cocaine dependence completely relies on self-perception but ignores the amount or duration of cocaine use, some subjects in the RCU group might be misclassified. ii) We employed hair toxicologies to quantify objectively illegal drug use in the last 3 to 6 months (depending on hair length) but had to rely on self-reports before this period of time. iii) The cross-sectional design of this study makes it impossible to determine the causal relationship between impulsivity and cocaine use.

In conclusion, the present study confirms previous findings of elevated trait impulsivity and novelty seeking scores in CU compared with controls. Given that both recreational cocaine use and dependent cocaine use were associated with higher trait impulsivity, it is not an exclusive feature of addicted cocaine use. Trait impulsivity was strongly associated with an increased number of ADHD and depression symptoms and correlated significantly with long-term cocaine intake parameters. By contrast, none of the behavioral motor impulsivity measures in this study showed significant group effects or correlated with cocaine use parameters. However, it remains unclear if there is a dissociation

between trait impulsivity and motor impulsivity or if the differences rather highlight difficulties in the operationalization and measurement of motor impulsivity. Furthermore, in accordance with the current literature, the correlations among the self-report impulsivity measures were high; however, self-reports were scarcely correlated with behavioral impulsivity task measures. Finally, although our results do not indicate any cocaine-related elevation of behavioral impulsivity in terms of motor or response inhibition, other studies have consistently reported increased behavioral impulsivity for DCU in terms of reward discounting (Heil et al., 2006; Hulka et al., 2013a).

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3.7 Supplementary material

3.7.1 Methods

sMethods 1: Recruitment and selection

The recruitment focused on the greater area of Zurich and lasted from January 2010 until January 2012. Participants were recruited via advertisements in local newspapers, online media, drug prevention and treatment centers, psychiatric hospitals, and by word of mouth. Eight-hundred-four prospective participants underwent a standardized telephone interview, whereof 240 subjects were considered to be eligible for the study at the University Hospital of Psychiatry in Zurich. All subjects were considered eligible to the study if they had sufficient German language skills and were aged between 18 and 60 years Forty-six participants had to be excluded afterwards due to hair analyses revealing illegal drug use not declared in the interviews (e.g., opioids, excessive MDMA use), a polytoxic drug use pattern, or lack of cocaine use. Furthermore, the data of four participants (3 controls, 1 cocaine user) could not be analyzed because of technical problems during the test session and 24 participants were excluded due to matching reasons (age, verbal IQ, and smoking) between groups (15 controls, 9 cocaine users). Hair samples were provided by 163 subjects, as hair analysis was not possible due to an insufficient amount of hair for two controls and one cocaine user.

sMethods 2: Urine and hair toxicologies

Urine toxicology analyses comprised the compounds/substances: tetrahydrocannabinol, cocaine, amphetamines, benzodiazepines, opioids, and methadone and were assessed by a semi-quantitative enzyme multiplied immunoassay method using a Dimension RXL Max (Siemens, Erlangen, Germany).

To characterize drug use over the last six months objectively, hair samples were collected and analyzed with Liquid chromatography-tandem mass spectrometry (LC-MS/MS). If participants' hair was long enough, one sample of six cm hair (from the scalp) was taken and subsequently divided into two subsamples of three cm length. The following compounds were assessed: cocaine, benzoylecgonine, ethylcocaine, norcocaine, amphetamine, methamphetamine, MDMA, MDEA, MDA, morphine, codeine, methadone EDDP (primary methadone metabolite), tramadol, and methylphenidate.

For our routine protocol for drugs of abuse analysis a three step washing procedure with water (2 minutes shaking, 15ml), acetone (2min., 10ml) and finally hexane (2min., 10ml) of hair was performed. Then the hair samples were dried at ambient temperatures, cut into small snippets and extracted in two steps, first with methanol (5ml, 16hours, ultrasonication) and a second step with 3 ml MeOH acidified with 50 µL hydrochloric acid 33 % (3 hours, ultrasonication). The extracts were dried and the residue reconstituted with 50 µL MeOH and 500 µL 0.2 mM ammonium formate (analytical

grade) in water. As internal standards deuterated standards of the following compounds were used, added as mixture of the following compounds: cocaine-d3, benzoylecgonine-d3, ethylcocaine-d3, morphine-d3, MAM-d3, codeine-d3, dihydrocodeine-d3, amphetamine-d6, methamphetamine-d9, MDMA-d5. MDEA-d6, MDA-d5, methadone-d9, EDDP-d3, methylphenidate-d9, tramadol-d3, oxycodone-d3, and ephedrine-d3. All deuterated standards were from ReseaChem (Burgdorf, Switzerland), the solvents for washing and extraction were of analysis grade and obtained from Merck (Darmstadt, Germany); LC-solvents were of HPLC grade and were obtained from Sigma Aldrich (Buchs, Switzerland).

The LC-MS/MS apparatus was an ABSciex QTrap 3200 (Analyst software Version 1.5, Turbo V ion source operated in the ESI mode, gas 1, nitrogen (50 psi); gas 2, nitrogen (60 psi); ion spray voltage, 3500V; ion source temperature, 450°C; curtain gas, nitrogen (20 psi) collision gas, medium), with a Shimadzu Prominence LC-system (Shimadzu CBM 20 A controller, two Shimadzu LC 20 AD pumps including a degasser, a Shimadzu SIL 20 AC autosampler and a Shimadzu CTO 20 AC column oven, Shimadzu, Duisburg, Germany). Gradient elution was performed on a separation column (Synergi 4µ POLAR-RP 80A, 150x2.0 with a POLAR-RP 4x2.0 Security Guard Cartridge, (Phenomenex, Aschaffenburg, Germany). The mobile phase consisted of 1mM ammonium formate buffer adjusted to pH 3,5 with formic acid (eluent A) and acetonitrile containing 1mM ammonium formate and 1 mM formic acid (eluent B). The Analysis was performed in MRM mode with two transitions per analyte and one transition for each deuterated internal standard, respectively.

sMethods 3: Impulsivity assessment

The *Barratt Impulsiveness Scale (BIS-11)* (Patton et al., 1995) is a commonly administered (Stanford et al., 2009), internally consistent (Patton et al., 1995), and well validated self-report measure for the assessment of trait impulsivity in both research and clinical settings (Reynolds et al., 2006). It consists of 30 items which, based on principal component analysis, can be reduced to three subscores labeled *attentional*, *motor*, and *non-planning* impulsivity and a *total score* (Patton et al., 1995).

The 240-item *Temperament and Character Inventory (TCI)* (Cloninger et al., 1999; Cloninger et al., 1993) is a questionnaire to assess basic personality dimensions of temperament and character. In this paper, we only analyzed the temperament factor novelty seeking (NS) because it is closely related to common impulsivity constructs. *The novelty seeking total score* describes a heritable pattern of behavior that comprises exploration in response to novelty and cues of reward, impulsive decision making, and quick loss of temper (Cloninger et al., 1993). It consists of 40 items that can be subdivided into four subscales (*exploratory excitability vs. stoic rigidity*, *impulsiveness vs. reflection*, *extravagance vs. reserve*, *disorderliness vs. regimentation*).

The *Rapid Visual Processing Task (RVP)* is a test of sustained attention from the Cambridge Neuropsychological Test Automated Battery (CANTAB; www.cantab.com) that has previously proved useful in several studies investigating cocaine use (Ersche et al., 2011; Soar et al., 2012; Vonmoos et al., 2013a). As attention is a cognitive component closely related to impulsive behavior and substance use (de Wit, 2009; Evenden, 1999; Garavan and Hester, 2007), and attentional impairments have previously been reported in recreational (Soar et al., 2012; Vonmoos et al., 2013a) as well as chronic cocaine users (Ersche et al., 2011; Jovanovski et al., 2005), we applied some impulsivity-related RVP parameters in order to increase the number impulsive behavior measures. In this regard, especially the *response bias B''* (response bias) reflects the tendency to respond regardless of the presence of a target and can therefore be interpreted as a measure for impulsive behavior (Nuechterlein, 1983). Additionally, impulsive behavior can be reflected by an increased number of *false alarms* paired with short response *latencies* (Ersche et al., 2011). Therefore, we analyzed these parameters separately and in combination, as we applied an *Impulsivity-score*, a composite index that reflects impulsivity on the dimension fast-inaccurate to slow-accurate and is calculated by subtracting standardized mean latency scores from errors scores (I-score=$z_{\text{false alarms}} - z_{\text{latency}}$)(Salkind and Wright, 1977). Both values were z-transformed on the basis of means and standard deviations of the control group.

The *stop-signal reaction task (SST)* (Logan, 1994; Verbruggen et al., 2008) is an operational measure for inhibitory motor control (Perry and Carroll, 2008) and has been widely used to study behavioral impulsivity in cocaine users (Ersche et al., 2012b; Fillmore and Rush, 2002; Hester and Garavan, 2004). The task requires subjects to respond quickly to pseudo-randomly presented visual go-signals on a computer screen (arrows to left and right with a probability of 50% each) and to inhibit a response shortly after the presentation of an auditory stop-signal (in 25% of all trials). First, we conducted a practice phase with 32 trials (not analyzed) and then 3 blocks of 64 trials (for further details to this task see Verbruggen et al. (2008). A staircase tracking procedure systematically varied the time between the go- and stop-signals until the stop-signal delay (SSD) was found at which the participant was able to inhibit the response on approximately 50%. The *stop signal reaction time (SSRT)* provided an estimation for response inhibition, a fundamental feature of impulsive motor behavior (de Wit, 2009). Additionally, we analyzed further stop-signal variables as recommended by Verbruggen et al. (2008): *percentage of correct inhibition, reaction time on go trials, percentage of correct responses on go trial*s, and *reaction time on signal-respond trials*.

sMethods 4: Group assignment for cofactors

Possible confounding factors of impulsivity were defined based on theoretical a priori considerations (Chaves et al., 2011; Perez de Los Cobos et al., 2011; Swendsen and Merikangas, 2000; Tziortzis et al., 2011; Vonmoos et al., 2013a; Wilson, 2007). To test the supposed relations of specific

confounding factors with impulsivity, a consolidated CU group was divided according to cofactor criteria and the two resulting CU subgroups were compared with the controls.

To test the influence of *recent cocaine use*, cocaine users were divided into users with positive (range: 217-24'888 ng/ml, mean: 3'873 ng/ml, SD: 6'461 ng/ml) and negative urine samples (**sTable 3**). Analogously, the influence of *recent cannabis use* was investigated by dividing cocaine users into users with positive (range: 60–726 ng/ml, mean: 125 ng/ml, SD: 143 ng/ml) and users with negative urine samples for THC. They were compared with controls featuring negative urine samples, as we excluded 10 controls displaying positive cannabis urine samples. *Age of onset* subgroups were divided according to a cut-off value of 18 years and *duration of cocaine use* subgroups were splitted according to a cut-off value of 10 years, separating the quarter of cocaine users in our sample, which had the longest duration of cocaine use. As *cocaine binge* is defined as out-of-control intake of large amounts of cocaine over an extended period of time (Mutschler et al., 2001), high *cocaine binge* was defined as an average cocaine use of at least 2g per occasion during the last 6 months. Cocaine user subgroups for *ADHD* (with/without ADHD,) and *depression* (no/at least mild, BDI ≥11, excluding 5 controls with BDI ≥11) were created according to predefined diagnostic criteria (Hautzinger et al., 1994; Roesler et al., 2004), for *craving* by median split (low/high, CCQ ≤16).

3.7.2 Results

sTable 1. Impulsivity measures (ANOVA, without correction for age)

Measure	n[a]	Controls	RCU	DCU	F	df, df_{err}	p	p, Sidak post-hoc			Cohen's d		
								Controls vs. RCU	Controls vs. DCU	RCU vs. DCU	Controls vs. RCU	Controls vs. DCU	RCU vs. DCU
Barratt Impulsiveness Scale (BIS-11)													
FI Attentional Impulsiveness	68/68/30	14.7 (3.1)	16.4 (3.9)	18.6 (4.1)	12.551	2, 163	**<.001**	**.02**	**<.001**	**.02**	.44	1.01	.58
FII Motor Impulsiveness	68/68/30	22.5 (3.9)	24.4 (4.5)	25.8 (5.8)	6.271	2, 163	**.002**	**.05**	**.003**	.42	.41	.70	.30
FIII Nonplanning Impulsivenes	68/68/30	26.3 (4.7)	27.9 (4.1)	28.9 (4.9)	4.438	2, 163	**.01**	.09	**.02**	.68	.37	.58	.22
BIS-11 Total score	68/68/30	63.4 (9.4)	68.7 (10.2)	73.3 (12.7)	10.425	2, 163	**<.001**	**.01**	**<.001**	.13	.48	.90	.42
Temperament and Character Inventory													
NS1 Exploratory excitability	67/68/28	7.4 (2.1)	8.1 (2.1)	7.1 (2.6)	2.319	2, 160	.10	.29	.87	.16	.28	.15	.43
NS2 Impulsiveness	67/68/28	4.8 (2.5)	5.9 (2.4)	5.9 (2.3)	4.313	2, 160	**.01**	**.02**	.16	1.00	.47	.42	.05
NS3 Extravagance	67/68/28	5.8 (2.3)	7.1 (1.7)	7.4 (1.8)	9.559	2, 160	**<.001**	**<.001**	**.001**	.85	.61	.76	.16
NS4 Disorderliness	67/68/28	4.4 (1.9)	5.8 (1.9)	5.5 (1.9)	10.465	2, 160	**<.001**	**<.001**	**.02**	.84	.73	.57	.16
Novelty seeking Total score	67/68/28	22.5 (6.3)	27.0 (4.9)	25.9 (4.8)	11.648	2, 160	**<.001**	**<.001**	**.02**	.78	.76	.58	.18
Rapid Visual Processing Task													
Response bias B"	67/68/30	.948 (0.1)	.938 (0.1)	.925 (0.1)	1.302	2, 162	.27	.74	.31	.77	.16	.35	.19
Mean latency (ms)	67/68/30	404.7 (86.2)	417.8 (92.3)	417.2 (91.9)	.412	2, 162	.66	.78	.89	1.00	.15	.14	.01
Total false alarms	67/68/30	1.3 (1.6)	1.9 (1.9)	2.2 (2.7)	2.951	2, 162	.06	.22	.08	.78	.30	.48	.19
Impulsivity-score	67/68/30	.00 (1.2)	.22 (1.3)	.46 (1.9)	1.189	2, 162	.31	.74	.35	.82	.16	.33	.17
Stop-Signal Task													
p(correct inhibition)	67/67/29	54.8 (9.1)	54.5 (11.0)	50.9 (15.1)	1.337	2, 160	.27	1.00	.32	.39	.03	.35	.32
RT on go trials (ms)	67/67/29	765.8 (187)	723.2 (199)	746.0 (188)	.819	2, 160	.44	.49	.96	.93	.22	.10	.12
p(correct responses on go trials)	67/67/29	94.4 (9.8)	91.9 (12.7)	93.6 (10.2)	1.501	2, 160	.23	.26	.99	.67	.29	.06	.23
RT on signal-respond trials (ms)	67/67/29	673.5 (177)	644.8 (191)	660.2 (163)	.421	2, 160	.66	.74	.98	.97	.16	.07	.09
Stop-signal reaction time, SSRT (ms)	65/65/27	298.2 (60.1)	276.8 (59.7)	293.5 (73.4)	2.021	2, 154	.14	.15	.98	.56	.34	.07	.27

Means and standard deviations. ANOVA (all groups). Significant p values are shown in bold.
[a] Sample size control group/RCU/DCU. For details see the methods part *Statistical analysis*.

sTable 2. Intercorrelation of cocaine use parameters in cocaine users

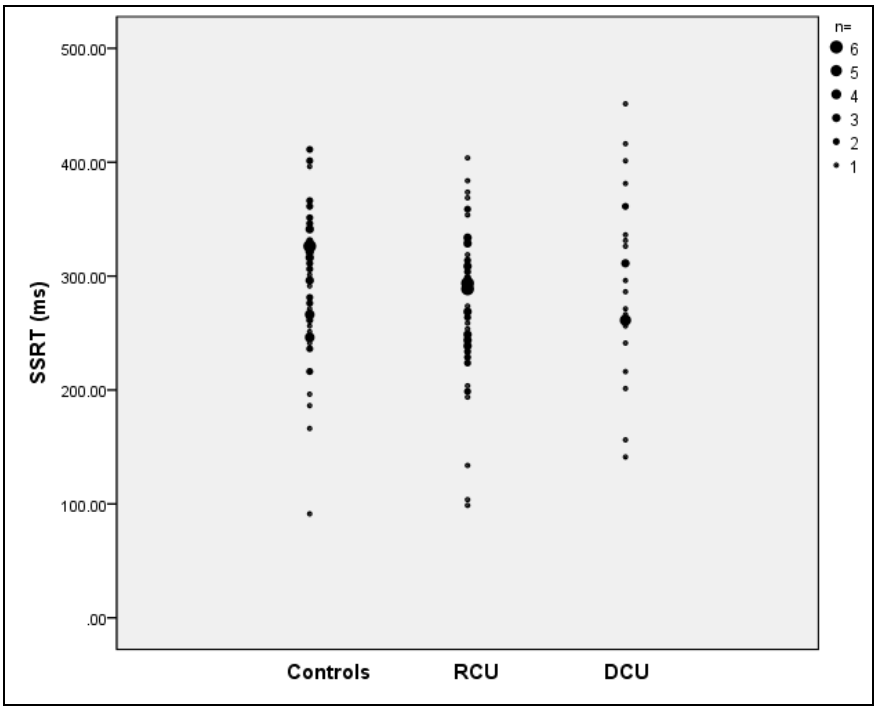
	2)	3)	4)	5)	6)	7)	8)	9)	10)	11)	12)
1) Cumulative dose (grams) log	*.24	*.22	***.57	.02	***.62	-.09	***.34	***.37	*.21*	***.39	***.36
2) Times per week	1	***.70	-.09	.09	.17	.15	.18	.14	*.23	.16	.18
3) Grams per week log		1	-.13	.04	.13	.13	.04	-.04	.18	-.01	.03
4) Years of use			1	-.03	.06	-.10	***.42	***.37	***.37	***.39	***.42
5) Age of onset				1	.07	-.17	.16	.20	.05	.17	.17
6) Maximum dose (grams/day)					1	-.09	.14	*.23	-.08	*.22	.16
7) CCQ sum score (0-70)						1	.03	-.01	-.03	.01	.02
8) Hair analysis Cocaine pg/mg							1	***.91	***.70	***.86	***1.00
9) Hair analysis Benzoylecgonine pg/mg								1	***.55	***.95	***.94
10) Hair analysis Cocaethylene pg/mg									1	***.62	***.68
11) Hair analysis Norcocaine pg/mg										1	***.89
12) Hair analysis $Cocaine_{total}$ pg/mg											1

Analyses only for cocaine users (n=98; Hair samples were voluntary and are deficient for 1 RCU).
Pearson's product-moment correlation. Significant correlations (two-tailed) are marked: *p<.05; **p<.01; ***p<.001.

sTable 3. Cofactor analyses

								p, Sidak post-hoc			Cohen's d		
	n	Controls	CU 1	CU 2	F	df, df_{err}	p	Controls vs CU 1	Controls vs CU 2	CU 1 vs CU 2	Controls vs CU 1	Controls vs CU 2	CU 1 vs CU 2
Urine toxicology Cocaine			*UP-*	*UP+*									
BIS-11 total	68/75/22	63.4 (1.3)	70.2 (1.2)	69.2 (2.2)	7.854	2, 161	**<.001**	**<.001**	.08	.97	.62	.53	.09
TCI NS	67/74/21	22.5 (0.7)	26.8 (0.6)	26.2 (1.2)	11.221	2, 158	**<.001**	**<.001**	**.02**	.97	.72	.63	.09
RVP B"	67/75/22	0.949 (0.0)	0.940 (0.0)	0.915 (0.0)	2.125	2, 160	.12	.80	.12	.34	.14	.51	.38
SSRT	65/71/21	298.1 (7.8)	283.5 (7.4)	276.1 (13.7)	1.397	2, 153	.25	.44	.42	.95	.23	.35	.12
Urine toxicology Cannabis			*UP-*	*UP+*									
BIS-11 total	58/75/22	62.8 (1.4)	69.4 (1.2)	72 (2.2)	6.048	3, 160	**<.001**	**.003**	**.003**	.88	.60	.84	.24
TCI NS	57/73/22	22.3 (0.7)	26.7 (0.6)	26.6 (1.2)	7.538	3, 157	**<.001**	**<.001**	**.01**	1.00	.74	.72	.02
RVP B"	57/75/22	0.948 (0.0)	0.936 (0.0)	0.928 (0.0)	.729	3, 159	.54	.89	.79	1.00	.18	.30	.12
SSRT	57/71/21	300.6 (8.4)	282.8 (7.5)	278.1 (13.7)	1.124	3, 152	.34	.52	.65	1.00	.28	.36	.08
Age of onset			*Onset >18*	*Onset ≤18*									
BIS-11 total	68/25/73	63.4 (1.3)	68.6 (1.2)	74.5 (2.2)	11.087	2, 162	**<.001**	**<.001**	**.01**	.06	1.02	.47	.55
TCI NS	67/24/72	22.5 (0.7)	26.5 (0.7)	27.2 (1.2)	11.451	2, 159	**<.001**	**.002**	**<.001**	.92	.80	.67	.13
RVP B"	67/25/73	0.949 (0.0)	0.94 (0.0)	0.916 (0.0)	2.054	2, 161	.13	.13	.83	.37	.50	.14	.36
SSRT	65/22/70	298.1 (7.8)	280.3 (7.6)	286.7 (14.0)	1.363	2, 153	.26	.86	.28	.97	.18	.28	.10
Duration of cocaine use			*≤10 years*	*>10 years*									
BIS-11 total	68/75/23	63.5 (1.2)	67.8 (1.2)	77.3 (2.3)	15.091	2, 162	**<.001**	**.04**	**<.001**	**.001**	.40	1.27	.87
TCI NS	67/73/23	22.5 (0.7)	26.1 (0.7)	28.5 (1.2)	12.861	2, 159	**<.001**	**<.001**	**<.001**	.26	.61	1.01	.41
RVP B"	67/75/23	0.949 (0.0)	0.928 (0.0)	0.953 (0.0)	1.998	2, 161	.14	.20	.99	.40	.31	.07	.37
SSRT	65/71/21	298.0 (7.8)	284.9 (7.6)	271.3 (14.7)	1.609	2, 153	.20	.55	.29	.81	.21	.43	.22
Binge			*low*	*high*									
BIS-11 total	68/74/24	63.4 (1.3)	69.8 (1.2)	70.8 (2.1)	8.131	2, 162	**<.001**	**.001**	**.01**	.97	.59	.67	.09
TCI NS	67/73/23	22.5 (0.7)	26.4 (0.6)	27.4 (1.1)	11.595	2, 159	**<.001**	**<.001**	**<.001**	.83	.66	.83	.17
RVP B"	67/74/24	0.949 (0.0)	0.940 (0.0)	0.915 (0.0)	2.389	2, 161	.09	.84	.09	.26	.12	.51	.39
SSRT	65/69/23	298.1 (7.8)	284.7 (7.5)	273.2 (13.1)	1.579	2, 153	.21	.52	.28	.83	.21	.40	.18
Craving			*low*	*high*									
BIS-11 total	68/52/46	63.4 (1.3)	68.8 (1.5)	71.5 (1.5)	8.911	2, 162	**<.001**	**.02**	**<.001**	.51	.49	.74	.24
TCI NS	67/51/45	22.5 (0.7)	27.3 (0.8)	25.9 (0.8)	12.180	2, 159	**<.001**	**<.001**	**.005**	.50	.82	.58	.24
RVP B"	67/52/46	0.949 (0.0)	0.941 (0.0)	0.927 (0.0)	1.509	2, 161	.224	.88	.23	.66	.12	.33	.21
SSRT	65/47/45	298.1 (7.8)	279.4 (9.2)	284.3 (9.4)	1.355	2, 153	.261	.32	.59	.98	.30	.22	.08
ADHD diagnosis			*w/out ADHD*	*with ADHD*									
BIS-11 total	68/76/22	63.4 (1.2)	67.2 (1.1)	80.0 (2.1)	24.384	2, 162	**<.001**	.06	**<.001**	**<.001**	.35	1.51	1.17
TCI NS	67/75/21	22.5 (0.7)	26.2 (0.6)	28.3 (1.2)	12.618	2, 159	**<.001**	**<.001**	**<.001**	.33	.63	.98	.35
RVP B"	67/76/22	0.949 (0.0)	0.936 (0.0)	0.928 (0.0)	1.071	2, 161	.34	.57	.51	.95	.20	.32	.12
SSRT	65/72/20	298.1 (7.8)	278.5 (7.4)	293.6 (14.0)	1.745	2, 153	.18	.19	.99	.72	.31	.07	.24
Depressive symptoms			*low*	*≥mild*									
BIS-11 total	63/69/29	63.7 (1.3)	67.7 (1.2)	75.8 (1.9)	13.997	2, 157	**<.001**	.08	**<.001**	**.001**	.36	1.10	.74
TCI NS	62/67/29	23.0 (0.7)	27.4 (0.7)	25.0 (1)	10.940	2, 154	**<.001**	**<.001**	.29	.12	.77	.34	.43
RVP B"	62/69/29	0.951 (0.0)	0.932 (0.0)	0.939 (0.0)	1.310	2, 156	.27	.29	.84	.94	.29	.18	.11
SSRT	60/65/27	297.4 (8.1)	275.9 (7.8)	295.9 (12.1)	2.071	2, 148	.13	.17	1.00	.43	.34	.02	.31

Means and standard errors. ANCOVA (all groups, corrected for age). Significant p values are shown in bold.
[a] Sample size control group/CU 1/CU 2. For details see the methods part *Statistical analysis*.



sFigure 1. SSRT analysis. Separated for control group (n=65), recreational cocaine user group (n=65), and dependent cocaine user group (n=27).

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4 Impairment in cocaine users is drug-induced but partially reversible: evidence from a longitudinal study

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MV collected, analyzed, and interpreted the data and wrote the manuscript. LMH, KHP, and FM contributed to the data acquisition and/or revised the first draft of the manuscript. MRB conducted the hair analyses. BBQ designed the study, contributed to the data analysis, and revised the manuscript.

4.1 Abstract

Objective. Cocaine users consistently display cognitive impairments. However, it is still unknown whether these impairments are cocaine-induced, predisposed, or both. Therefore, we examined the relation between objectively changing intensity of cocaine use and the development of cognitive functioning within 1 year.

Methods. The present data were collected as part of the longitudinal Zurich Cocaine Cognition Study ($ZuCo^2St$). Forty-eight psychostimulant-naïve controls and 57 cocaine users (19 with increased, 19 with decreased, and 19 with unchanged cocaine use) were eligible for analysis. At baseline and after a one-year follow-up, cognitive performance was measured by a global cognitive index and 4 neuropsychological domains (attention, working memory, declarative memory, executive functions), calculated from 13 parameters of a broad neuropsychological test battery. Intensity of cocaine use was objectively determined by quantitative 6-month hair toxicology at both test sessions.

Results. Substantially increased cocaine use within 1 year led to deteriorated cognitive performance primarily in the working memory. By contrast, decreased cocaine use generally improved cognition and showed the strongest enhancement in working memory and declarative memory. Users who ceased taking cocaine seemed to recover completely, attaining a cognitive performance level similar to that of the control group.

Conclusions. These longitudinal data suggest that cognitive impairment might be partially cocaine-induced but reversible within 1 year. The reversibility indicates that neuroplastic adaptations underlie cognitive changes in cocaine users, which are potentially modifiable in psychotherapeutical or pharmacological interventions. These findings imply that abstinence might be the ideal way to enhance cognitive performance in stimulant users.

4.2 Introduction

The annual number of cocaine users is currently estimated at 17 million people worldwide (United Nations Office on Drugs and Crime, 2013). Because of its high addictive potential and harmful effects on mental and physical well-being (Degenhardt, 2012; Nutt et al., 2007), the use of cocaine is a major public health issue with substantial societal and economic costs (Degenhardt, 2012).

Accumulating evidence suggests that dependent (Goldstein et al., 2004; Jovanovski et al., 2005; Vonmoos et al., 2013a; Woicik et al., 2009) and also recreational (Colzato et al., 2009a; Reske et al., 2010b; Soar et al., 2012; Vonmoos et al., 2013a) cocaine use is associated with broad neuropsychological impairment. Remarkably, 30% of dependent users, and even 12% of recreational users, exhibit clinically relevant global cognitive impairment (Vonmoos et al., 2013a). Studies have shown deficits in attention, working memory, and declarative memory in chronic cocaine users, whereas the heterogeneous concept of executive functions has yielded mixed results (Jovanovski et al., 2005; Vonmoos et al., 2013a). We recently demonstrated that cocaine users additionally display inferior social cognition, including emotional empathy, mental perspective-taking, and social decision-making (Hulka et al., 2013a; Preller et al., 2013a). A worse social cognitive performance was correlated with a smaller social network and more criminal offenses in cocaine users (Preller et al., 2013a), pointing to the importance of cognitive health for social and occupational functioning in drug users as in psychiatric patients (Lee et al., 2013). Moreover, neuropsychological performance predicts the attainment of treatment objectives and the likelihood of treatment dropout in substance users (Teichner et al., 2001; Teichner et al., 2002).

Today, it is still unclear whether these cognitive impairments are cocaine-induced, predisposed, or both (Rogers and Robbins, 2001). Studies on chronic cocaine self-administration in rhesus monkeys suggest that some alterations in attention, learning, and working memory might be cocaine-induced (Gould et al., 2012; Liu et al., 2008; Porter et al., 2011). In contrast to these animal studies, research with human cocaine users has focused on the effects of drug abstinence on cognition. The few and preliminary cross-sectional (Bolla et al., 1999; De Oliveira et al., 2009) and longitudinal (Bauer, 1996; Bolla et al., 2000; Di Sclafani et al., 2002; van Gorp et al., 1999) studies either indicate persisting neuropsychological impairment in attention (Bauer, 1996), declarative memory (van Gorp et al., 1999), and executive function (De Oliveira et al., 2009), or hint at some recovery effects in working (Di Sclafani et al., 2002) and verbal (De Oliveira et al., 2009) memory. However, these results should be interpreted with caution because cocaine use in these studies was self-reported and solely controlled with drug urine tests but not hair toxicology analyses, which would have enabled a reliable detection of drug use during the last months. Moreover, these studies had relatively brief follow-up intervals with strongly varying abstinence durations (1 week to 6 months) and several studies reported only minimal information on the severity of drug use. To date, no longitudinal study has investigated the effects of escalating cocaine use on cognition.

Accordingly, we aimed to overcome these limitations by means of a longitudinal study specifically investigating the impact of decreased and increased cocaine use on cognitive performance at a one-year interval. Therefore, we categorized cocaine users in the Zurich Cocaine Cognition Study ($ZuCo^2St$) as *decreasers*, *stable users*, or *increasers* after the one-year follow-up. We then compared the course of cognitive performance only between *decreasers* and *increasers*, whose test scores were normalized to the test-retest effects of a large psychostimulant-naïve control group that was also assessed twice. Because we were interested in the specific effects of cocaine, relatively pure users with very little co-use of other illegal drugs were initially recruited. To assess objectively the initial severity and change in cocaine use and to control for co-use of other drugs, we performed quantitative hair and urine toxicology analyses at baseline and follow-up. Because we recently reported strong dose-effect correlations between several cocaine use parameters and cognitive performance in cocaine users from the cross-sectional part of this study (Vonmoos et al., 2013a), and based on previous animal studies suggesting that cognitive impairment in cocaine users might be drug-induced (Gould et al., 2012; Liu et al., 2008; Porter et al., 2011), we hypothesized that escalating cocaine use is associated with further cognitive impairment. Based on data suggesting that long-term cocaine abstinence of cocaine might be associated with partial recovery of neuropsychological performance (De Oliveira et al., 2009; Di Sclafani et al., 2002; van Gorp et al., 1999), we expect to find partially improved cognition in cocaine users with considerably decreased or ceased cocaine consumption.

4.3 Method

4.3.1 Participants

From a cross-sectional sample of 234 participants, 48 psychostimulant-naïve controls and 57 cocaine users were included in the longitudinal study (recruitment and selection details **sMethods 1**). At baseline, general exclusion criteria were neurological disorders or head injuries, medical diseases, and medication affecting the central nervous system. Controls were also excluded if they displayed current or previous *DSM-IV* Axis I psychiatric disorders (except for nicotine addiction), and regular illegal drug use (>15 occasions lifetime, except for recreational cannabis use). Exclusion criteria for cocaine users were use of opioids, polytoxic drug use patterns, and *DSM-IV* Axis I adult psychiatric disorders – except for cocaine, cannabis, nicotine, and alcohol abuse/dependence; history of affective disorders (current major depression was excluded); and attention deficit hyperactivity disorder (ADHD). Inclusion criteria for cocaine users were cocaine use of >0.5g per month, cocaine as primary drug, and an abstinence duration of <6 months at baseline.

Participants were asked to abstain from illegal substances for at least 72h and from alcohol for 24h before test sessions. Compliance with these instructions was controlled using urine screenings (semi-quantitative enzyme multiplied immunoassay method)(Vonmoos et al., 2013a). Drug use severity was assessed by 6-month hair toxicology analyses (liquid chromatography-tandem mass spectrometry, LC-MS/MS)(Vonmoos et al., 2013a). The study was approved by the Cantonal Ethics Committee of Zurich. All participants provided written informed consent and received compensation for their participation.

4.3.2 Group assignment

The decisive criterion for replicable group assignment was a combination of absolute and relative changes in cocaine concentration in hair samples between baseline (t1) and follow-up (t2)(Singer and Willett, 2003). The absolute criterion was based on a shift in cocaine concentration of at least ±500 pg/mg, which is a commonly accepted cut-off value for reliably detection of cocaine use (Bush, 2008; Society of Hair Testing, 2004). The relative criterion was based on a minimal increase of 20% or a minimal decrease of 10% in the robust hair toxicology parameter $Cocaine_{total}$ (=Cocaine+Benzoylecgonine+Norcocaine)(Hoelzle et al., 2008). According to these criteria, cocaine users were divided into 3 groups of similar size: 19 cocaine *increasers* consumed substantially more cocaine at t2 (mean increase +30’429 pg/mg [+1139%], range +533 to +268’500 pg/mg [+20% to +5374%], SD 61’931 pg/mg), whereas 19 cocaine *decreasers* consumed substantially less cocaine (mean decrease -10’646 pg/mg [-69%], range -116’855 to -625 pg/mg [-100% to -12%], SD 26’746

pg/mg), and 19 users with a relatively stable cocaine use pattern did not meet both criteria, and, thus, were not further analyzed.

4.3.3 Procedure

The test procedure was similar in t1 and t2. Trained psychologists conducted the Structured Clinical Interview for *DSM-IV* (SCID-I)(American Psychiatric Association, 1994). Drug use was assessed with a structured and standardized Interview for Psychotropic Drug Consumption (Quednow et al., 2004). Cognitive performance was assessed with a neuropsychological test battery comprising 3 tests of the Cambridge Neuropsychological Test Automated Battery (CANTAB, www.cantab.com): Rapid Visual Processing (RVP), Spatial Working Memory (SWM), Paired Associates Learning (PAL); a German version of the Rey Auditory Verbal Learning Test (RAVLT)(Helmstaedter et al., 2001); and the Letter Number Sequencing Task (LNST)(Wechsler, 1997). At t2, parallel test-versions were used for the PAL, RAVLT, and LNST. In contrast to the cross-sectional analysis, we excluded the CANTAB Intra/Extradimensional Set Shifting (IED) from the longitudinal analysis because of an evident ceiling effect at t1 (Vonmoos et al., 2013a).

Analogous to the cross-sectional study (Vonmoos et al., 2013a), 13 predefined main cognitive test parameters were *z*-transformed on the basis of means and standard deviations of the control group (n=48) at baseline. If necessary, test scores were reversed so that high scores always indicated better cognitive performance. Test parameters were reduced to 4 cognitive domains (attention, working memory, declarative memory, and executive functions, **sMethods 2**). Furthermore, the 4 *z*-scored domains were equally integrated into a broad global cognitive index (GCI).

4.3.4 Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics 19.0. Effect sizes were calculated with G*Power 3.1 (Faul et al., 2007). Frequency data were analyzed by means of Pearson's chi-square test. Group differences in cognitive test scores at t1 and t2 were analyzed by analyses of variance (ANOVA). To assess longitudinal effects in cognitive parameters, change scores between t1 and t2 ($\Delta_{t2\text{-}t1}$) were calculated and analyzed with paired Student's *t*-tests separately in each group. Because we expected inevitable test-retest effects, we corrected the user groups' change scores using the mean change score of the control group. Accordingly, change score ($\Delta_{t2\text{-}t1}$) group effects were analyzed only for the 2 user groups with independent Student *t*-tests. Change score group effects for *increaser* and *decreaser* subgroups were examined with ANOVA. To relate cognitive change scores to changing cocaine use during the testing interval, Pearson product-moment correlation analyses (two-tailed) were conducted in the cocaine user group.

4.4 Results

4.4.1 Demographic characteristics and drug use

Controls, *increasers*, and *decreasers* did not differ regarding demographic data and time interval between t1 and t2 (**Table 1**). However, both cocaine user groups displayed significantly higher BDI and ADHD-self-report sum scores than controls. As intended, hair samples and cumulative doses revealed a clear dominance of cocaine compared with other illegal drugs (**sTable 1, sTable 2**). At t1, *increasers* and *decreasers* displayed similar cocaine hair concentrations; however, at t2 *increasers* showed an approximately 10-fold higher concentration of cocaine than *decreasers*. Whereas hair analyses for *increasers* showed a 4-fold increase between t1 and t2, hair analyses for *decreasers* displayed a mean reduction of ~75% (**sFigure 1**). In contrast to baseline, none of the self-reported cocaine use parameters correlated with hair cocaine concentrations in the follow-up, highlighting the importance of objective drug use measures in longitudinal studies (**sTable 3**).

Table 1. Demographic data and pattern of cocaine use.

	t1						t2					
	Controls (n=48)	Cocaine Increasers (n=19)	Cocaine Decreasers (n=19)	F/χ^2/T	df,df_{err}	p	Controls (n=48)	Cocaine Increasers (n=19)	Cocaine Decreasers (n=19)	F/χ^2/T	df,df_{err}	p
Age, y	30.3 (±8.9)	31.5 (±9.4)	31.4 (±8.3)	.19[a]	2,83	.82						
Sex (f/m)	16/32	3/16	5/14	2.11[b]	2	.35						
Verbal IQ (MWT-B)[d]	107.6 (±10.0)	102.9 (±9.7)	103.8 (±7.1)	2.20[a]	2,83	.12						
Education, y	10.8 (±1.8)	10.4 (±1.8)	10.0 (±1.5)	1.30[a]	2,83	.28						
ADHD-SR score (0-22)	7.7 (±5.2)	13.5 (±9.4)**	14.1 (±6.8)**	8.83[a]	2,83	**<.001**						
ADHD DSM IV (y/n)[e]	0/48	4/15	3/16	7.02[b]	2	**.03**						
Weeks between t1 and t2	58.2 (±10.1)	59.3 (±12.1)	61.9 (±14.5)	.69[a]	2,83	.50						
Smoking (y/n)[f]	37/11	14/5	14/5	.13[b]	2	.94	40/8	15/4	13/6	1.83[b]	2	.40
BDI score (0-63)	3.5 (±3.3)	7.3 (±8.0)*	8.7 (±6.5)**	7.53[a]	2,83	**<.001**	2.3 (±3.3)	8.1 (±8.4)***	6.4 (±6.0)*	9.21[a]	2,83	**<.001**
BDI depression (y/n)[g]	0/48	1/18	1/18	2.59[b]	2	.27	0/48	2/17	1/18	4.71[b]	2	.09
Cocaine												
Times per week[h]	-	1.6 (1.8)	1 (1.3)	1.37[c]	1,36	.25	-	1.1 (0.8)	0.3 (0.3)	14.80[c]	1,36	**<.001**
Grams per week[h]	-	2 (2.5)	1.7 (2.3)	.17[c]	1,36	.68	-	1.6 (2.5)	0.4 (0.4)	4.76[c]	1,36	**.04**
Years of use	-	7 (5.5)	8.2 (5.4)	.46[c]	1,36	.50	-	8.9 (5.4)	9.7 (5.2)	.21[c]	1,36	.65
Max. dose (grams/day)	-	4.7 (4.4)	5.9 (6.4)	.51[c]	1,36	.48	-	3.7 (2.5)	3.1 (2.8)	.40[c]	1,36	.53
Cumulative dose (grams)	-	1182 (1635)	3698 (8585)	1.57[c]	1,36	.22	-	91 (119)	49 (89)	1.56[c]	1,36	.22
Last consumption (days)	-	18.5 (25.1)	16.8 (14.6)	.06[c]	1,36	.77	-	7.0 (6.3)	81.4 (145.1)	4.98[c]	1,36	**.03**
Craving for cocaine (0-70)i	-	19.8 (±9.5)	17.7 (±7.2)	.79[c]	1,36	.44	-	20.5 (±10.8)	15.8 (±6.2)	1.66[c]	1,29	.11
Cocaine dependence (y/n)[j]	-	7/12	4/15	1.15[b]	1	.28	-	8/11	0/19	10.13[b]	1	**.001**
Hair analysis, pg/mg												
$Cocaine_{total}$	-	10258 (29236)	14885 (32227)	.21[c]	1,36	.65	-	40687 (76091)	4239 (8187)	4.31[c]	1,36	**.05**
Cocaine	-	8181 (23283)	11382 (23934)	.17[c]	1,36	.68	-	31707 (56491)	3131 (5884)	4.81[c]	1,36	**.03**
Benzoylecgonine	-	1877 (5456)	3125 (7565)	.34[c]	1,36	.56	-	8339 (19633)	1017 (2194)	2.61[c]	1,36	.11
Cocaethylene	-	1008 (2815)	903 (2826)	.01[c]	1,36	.91	-	1169 (2109)	334 (976)	2.45[c]	1,36	.13
Norcocaine	-	200 (508)	377 (781)	.69[c]	1,36	.41	-	641 (1397)	91 (130)	2.92[c]	1,36	.10
Urine toxicology (neg/pos)[k]	48/0	14/5	16/3	1.50[b]	2	.47	48/0	7/12	18/1	14.24[b]	2	**<.001**

Means and standard deviations. Significant p values are shown in bold.
[a] ANOVA (all groups, with significant Sidak post-hoc test vs. control group: *p<.05; **p<.01; ***p<.001).
[b] χ^2 test (all groups/cocaine users only) for frequency data.
[c] Independent t-test (cocaine users only).
[d] Verbal IQ was assessed by the Mehrfachwahl Wortschatz Intelligenztest (Lehrl, 1999).
[e] ADHD-SR, ADHD self rating scale (cut-off DSM-IV criteria)(Roesler et al., 2004).
[f] Smoking habits were assessed by the Fagerstroem Test of Nicotine Dependence (Heatherton et al., 1991).
[g] BDI, Beck Depression Inventory (cut-off ≥18)(Hautzinger et al., 1994).
[h] Average use during the last 6 months.
[i] Craving for cocaine was assessed by the Brief-CCQ (Sussner et al., 2006).
[j] Cocaine dependence criteria according to DSM-IV (SCID-I)(American Psychiatric Association, 1994).
[k] Cut-off value for cocaine = 150 ng/ml (Substance Abuse and Mental Health Services Administration, 2008).

4.4.2 Test scores at baseline

As previously demonstrated in the cross-sectional sample of this study (Vonmoos et al., 2013a), ANOVAs showed significant group effects for the GCI, both memory domains, and the executive function but only a statistical trend for attention (**Table 2**), indicating moderate to strong cognitive impairments in both cocaine user groups compared with controls (Cohen's *d*=0.47–0.79). *Increaser* and *decreaser* did not substantially differ in the GCI (*p*=.99, *d*=0.08) and all four domains (*p*≥.94, *d*≤0.14).

Table 2. Cognitive test scores at the baseline (t1) and the one-year follow-up (t2).

	t1						t2					
	Controls (n=48)	Cocaine Increasers (n=19)	Cocaine Decreasers (n=19)	F[a]	df,df$_{err}$	p	Controls (n=48)	Cocaine Increasers (n=19)	Cocaine Decreasers (n=19)	F[a]	df,df$_{err}$	p
Global Cognitive Index	0.00 (0.54)	-0.52 (0.77)*	-0.46 (0.73)*	6.26	2,83	**.003**	0.24 (0.58)	-0.36 (0.84)**	-0.07 (0.72)	5.85	2,83	**.004**
Neurocognitive domains												
Attention	0.00 (0.78)	-0.45 (0.85)	-0.41 (0.87)	2.94	2,83	.06	0.29 (0.84)	-0.18 (0.91)	0.04 (0.83)	2.19	2,83	.12
Working memory	0.00 (0.70)	-0.46 (0.91)	-0.47 (0.69)	4.09	2,83	**.02**	0.24 (0.64)	-0.44 (0.80)**	-0.14 (0.69)	7.17	2,83	**.001**
Declarative memory	0.00 (0.76)	-0.60 (1.12)	-0.44 (1.11)	3.42	2,83	**.04**	0.20 (0.66)	-0.53 (1.19)*	-0.02 (1.21)	4.10	2,83	**.02**
Executive functions	0.00 (0.70)	-0.58 (1.11)*	-0.52 (0.96)	4.36	2,83	**.02**	0.25 (0.79)	-0.31 (1.19)	-0.18 (0.65)	3.46	2,83	**.04**
Attention												
RVP Discrimination perf. A'	0.92 (0.04)	0.90 (0.04)	0.90 (0.04)	1.92	2,83	.15	0.93 (0.04)	0.91 (0.04)	0.92 (0.04)	2.00	2,83	.14
RVP Total hits	18.35 (4.21)	16.26 (4.62)	16.79 (4.38)	1.95	2,83	.15	19.98 (4.19)	17.79 (4.77)	18.63 (3.85)	2.02	2,83	.14
RAVLT Supraspan trial 1	9.38 (2.47)	8.47 (2.2)	8.26 (2.18)	1.99	2,82	.14	9.66 (2.43)	8.68 (2.08)	9.37 (2.87)	1.06	2,82	.35
Working memory												
LNST Score	15.54 (2.92)	14.00 (3.48)	14.00 (2.56)	2.84	2,83	.06	15.69 (3.10)	13.74 (3.11)	14.32 (2.94)	3.27	2,83	**.04**
SWM Total errors	20.31 (16.38)	27.11 (19.75)	26.95 (19.77)	1.49	2,83	.23	13.52 (14.14)	25.53 (15.99)*	20.84 (15.64)	4.94	2,83	**.009**
PAL First trial memory score	15.48 (3.87)	13.84 (4.26)	13.58 (2.43)	2.45	2,83	.09	16.42 (3.08)	13.95 (3.63)*	15.63 (3.70)	3.71	2,83	**.03**
Declarative memory												
RAVLT Learning perf. (?trials 1-5)	63.38 (6.53)	57.37 (9.66)*	57.84 (10.30)*	5.19	2,82	**.008**	64.40 (6.64)	58.26 (10.55)*	62 (10.00)	3.63	2,82	**.03**
RAVLT Adjusted recognition p(A)	0.87 (0.11)	0.84 (0.19)	0.85 (0.14)	.54	2,82	.59	0.87 (0.11)	0.84 (0.16)	0.86 (0.18)	.31	2,82	.73
RAVLT Delayed recall trial 7	13.19 (2.00)	12.00 (3.04)	11.89 (2.92)	2.66	2,82	.08	13.66 (1.77)	12.05 (3.66)	13.42 (2.39)	3.00	2,82	.06
PAL Total errors adjusted	11.96 (13.76)	19.32 (15.73)	15.00 (12.11)	1.95	2,83	.15	6.96 (6.69)	18.47 (16.17)**	11.74 (17.59)	6.17	2,83	**.003**
PAL Total trials adjusted	8.71 (3.44)	10.74 (4.01)	9.63 (3.29)	2.31	2,83	.11	7.88 (2.20)	10.37 (4.09)**	8.47 (3.61)	4.62	2,83	**.01**
Executive functions												
SWM Strategy score	32.27 (6.13)	33.53 (6.28)	33.00 (5.45)	.32	2,83	.72	29.54 (6.03)	31.47 (6.81)	32.89 (4.41)	2.40	2,83	.10
RAVLT Recall consistency in %	93.05 (5.75)	87.54 (9.84)*	87.70 (8.61)*	5.52	2,82	**.006**	93.43 (6.34)	88.76 (10.97)	91.61 (6.06)	2.61	2,82	.08

Means and standard deviations. Significant p values are shown in bold.
[a] ANOVA (all groups, with significant Sidak post-hoc test vs. control group: *p<.05; **p<.01; ***p<.001).
Global cognitive index and cognitive domain scores are z-transformed values.

4.4.3 Change scores between baseline and follow-up

All groups displayed an improvement from t1 to t2 on the GCI, all domains, and the majority of the single parameters (**Table 2**). Whereas these improvements on the cognitive domains are substantial and mostly significant in controls (*p*=.02–.00005, *d*=0.36–0.65) and *decreasers* (*p*=.07–.002, *d*=0.45–0.86), they are only small to moderate in *increasers* (*p*=.91–.07, *d*=-0.03–-0.44).

In pre-post comparisons with paired *t*-tests corrected for the test-retest effects (**Table 3**, **Figure 1**), *increasers* showed a significant cognitive decline in working memory (*d*=-0.52) and small effect sizes for a decline in declarative memory (*d*=-0.15) and the GCI (*d*=-0.20). By contrast, improvements for the *decreasers* were not significant but revealed small to moderate effect sizes in attention (*d*=0.22), working memory (*d*=0.22), declarative memory (*d*=0.29), and the GCI (*d*=0.32).

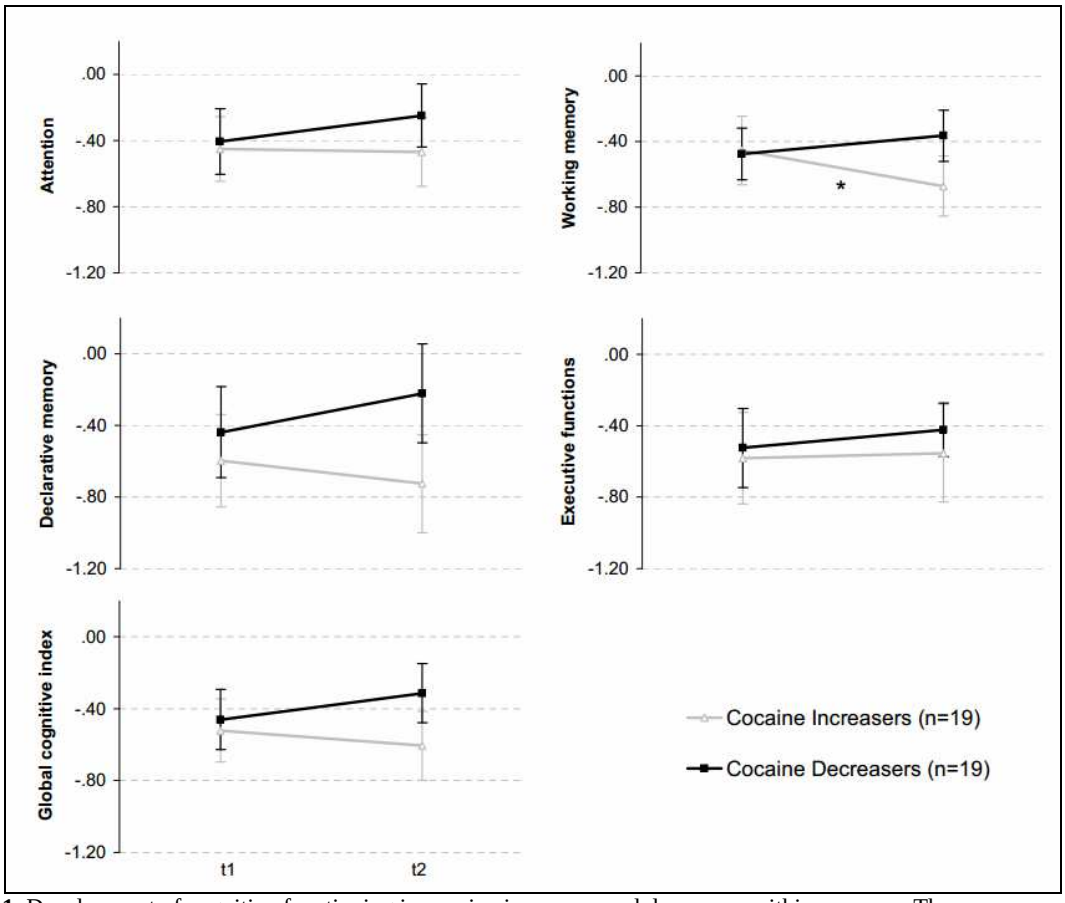

Figure 1. Development of cognitive functioning in cocaine increasers and decreasers within one year. The *z*-scores and SE for the cognitive domains (values at t2 are corrected for the test-retest effect). *indicates a significant (t_{18}=-2.28, p=.035) cognitive change from the baseline (t1) to the one-year follow-up (t2).

Independent *t*-tests comparing the test-retest corrected GCI and domain change scores ($\Delta_{t2\text{-}t1}$) between the two user groups showed a significant and strong group effect on working memory (t_{36}=2.24, p<.05, d=0.73). Furthermore, *increaser* and *decreaser* differed moderately in the GCI (t_{36}=1.59, p=.12, d=0.52) and declarative memory change scores (t_{36}=1.32, p=.19, d=0.43).

Additional correlation analyses within a consolidated group of *increasers* and *decreasers* indicated a significant association between cumulative cocaine dose during the testing interval and change scores in attention (**sTable 4**). A significant linkage between age of cocaine use onset and working memory improvement was found in *decreasers* (**sFigure 2**), indicating an association between early onset of cocaine use and reduced cognitive recovery.

Table 3. Cognitive change scores between the baseline (t1) and the one-year follow-up (t2).

	Cocaine Increasers (n=19)					Cocaine Decreasers (n=19)				
	Change score	T[a]	df	p	Cohen's d	Change score	T[a]	df	p	Cohen's d
Global Cognitive Index	-0.09 (0.44)	-.85	18	.41	-.20	0.14 (0.45)	1.39	18	.18	.32
Neurocognitive domains										
Attention	-0.02 (0.61)	-.14	18	.89	-.03	0.16 (0.73)	.94	18	.36	.22
Working memory	-0.22 (0.43)	-2.28	18	**.03**	-.52	0.10 (0.47)	.95	18	.36	.22
Declarative memory	-0.13 (0.85)	-.66	18	.52	-.15	0.22 (0.75)	1.25	18	.23	.29
Executive functions	0.03 (0.76)	.15	18	.88	.03	0.10 (0.77)	.57	18	.57	.13
Attention										
RVP Discrimination perf. A'	0.00 (0.03)	-.18	18	.86	-.04	0.00 (0.04)	.31	18	.76	.07
RVP Total hits	-0.10 (3.10)	-.14	18	.89	-.03	0.22 (3.61)	.26	18	.80	.06
RAVLT Supraspan trial 1	-0.07 (2.12)	-.14	18	.89	-.03	0.83 (2.85)	1.27	18	.22	.29
Working memory										
LNST Score	-0.41 (2.98)	-.60	18	.56	-.14	0.17 (2.52)	.29	18	.77	.07
SWM Total errors	5.21 (12.53)	1.81	18	.09	.42	0.69 (13.45)	.22	18	.83	.05
PAL First trial memory score	-0.83 (2.81)	-1.29	18	.21	-.30	1.12 (4.09)	1.19	18	.25	.27
Declarative memory										
RAVLT Learning perf. (? trials 1-5)	-0.13 (8.95)	-.06	18	.95	-.01	3.14 (7.60)	1.80	18	.09	.41
RAVLT Adjusted recognition p(A)	0.01 (0.22)	.13	18	.90	.03	0.02 (0.13)	.52	18	.61	.12
RAVLT Delayed recall trial 7	-0.42 (2.57)	-.70	18	.49	-.16	1.06 (2.14)	2.15	18	**.05**	.49
PAL Total errors adjusted	4.16 (9.69)	1.87	18	.08	.43	1.74 (13.26)	.57	18	.58	.13
PAL Total trials adjusted	0.46 (2.50)	.81	18	.43	.19	-0.32 (3.22)	-.44	18	.67	-.10
Executive functions										
SWM Strategy score	0.68 (3.50)	.84	18	.41	.19	2.62 (4.71)	2.43	18	**.03**	.56
RAVLT Recall consistency in %	0.84 (8.04)	.46	18	.65	.10	3.53 (6.93)	2.22	18	**.04**	.51

Means and standard deviations are corrected for the test-retest effect of the control group. Significant p values are shown in bold.
[a] Paired t-tests in each group.
Global cognitive index and cognitive domain scores are z-transformed values.

4.4.4 Test scores at follow-up

In contrast to baseline, *decreasers* performed slightly, albeit non-significantly better than *increasers* on the GCI (*d*=0.37), all domains (*d*=0.14–0.42), and each single parameter (*d*=0.14–0.42)(**Table 2**). Accordingly, the domain differences between *decreasers* and controls were reduced to non-significant small to moderate effect sizes (*d*=0.24–0.59). Controls and *increasers* still differed significantly in the GCI (*d*=0.86), working memory (*d*=0.95), and declarative memory (*d*=0.78).

4.4.5 Impact of ceased and strongly intensified cocaine use

To investigate the impact of ceased or strongly intensified cocaine use, we matched and split cocaine *increaser* (low/high; cut-off $\Delta_{t2\text{-}t1}$ $Cocaine_{total}$ <10'000 pg/mg), and *decreaser* subgroups (ceased use/ongoing use; cut-off $Cocaine_{total}$ at t2 <550 pg/mg, whereby Cocaine at t2 <500 pg/mg (Bush, 2008; Society of Hair Testing, 2004))(**sTable 5**). Paired *t*-tests showed a significant and strongly improved GCI (test-retest corrected, t_7=2.42, p<.05, d=0.86) for cocaine users who ceased use, resulting in a follow-up test score similar to the control group (**Figure 2a**). By contrast, *decreasers* with ongoing cocaine use did not show a markedly changed GCI (t_{10}=0.25, p=.81, d=0.07), whereas

the low and high *increaser* groups both displayed small to moderate decrements in global cognitive test performance (low t_{10}=-0.30, p=.77, d=-0.09, high t_7=-0.99, p=.35, d=-0.35).

Regarding working memory, similar but less pronounced trends were found for cocaine users who ceased their use (d=0.24), continued but decreased their use (d=0.19) and increased their use (d_{high}=-0.38, d_{low}=-0.62) cocaine users (**Figure 2b**).

A comparison of cocaine *increasers* with positive (n=12) and negative urine samples (n=7) at follow-up did not reveal a significant group effect for the GCI change score (t_{17}=0.42, p=.68, d=0.20), indicating that recent cocaine use did not explain the decline in test performance (see also **sFigure 3**).

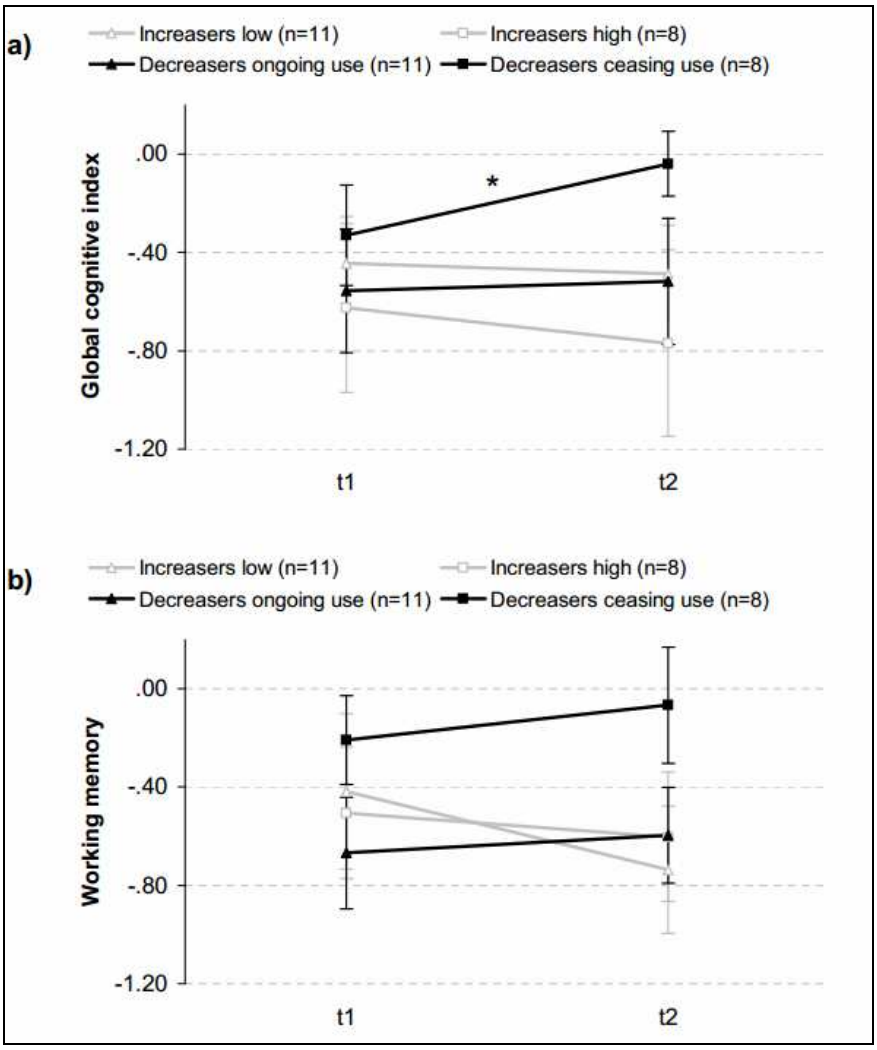

Figure 2. Cognitive functioning in low/high cocaine increasers and decreasers with ongoing/ceased cocaine use within one year. The *z*-scores and SE for (a) the GCI and (b) the working memory (values at t2 are corrected for the test-retest effect). *indicates a significant (t_7=-2.42, p=.046) cognitive change from the baseline (t1) to the one-year follow-up (t2).

4.5 Discussion

This longitudinal study is the first to investigate the development of cognitive performance as a result of objectively quantified changes in cocaine use patterns within a one-year period. Hair toxicology analyses allowed a precise drug use quantification to detect changes across the testing interval and ensured the inclusion of participants with little polytoxic drug use.

This study yielded several major findings: First, *increased* cocaine use was associated with additional cognitive decline within 1 year, particularly in working memory, thereby supporting the hypothesis that these cognitive impairments were partially cocaine-induced, as recent animal studies have implied (Gould et al., 2012; Liu et al., 2008; Porter et al., 2011). This finding is also in line with previous cross-sectional studies showing that the extent, duration, and amount of cocaine intake are linked to the severity of cognitive dysfunction (Bolla et al., 1999; Colzato et al., 2007; Vonmoos et al., 2013a). Second, *decreased* cocaine use within 1 year led to improved cognitive performance, primarily in working memory and declarative memory, thus confirming the assumption from previous cross-sectional and longitudinal studies that cognitive consequences from crack cocaine use might be partially reversible (De Oliveira et al., 2009; Di Sclafani et al., 2002). Users who completely ceased their cocaine consumption recovered entirely and attained a similar cognitive performance as controls in the follow-up. The reversibility of cognitive deficits after sustained abstinence suggests that neuroplastic adaptations might be restored if the repeated pharmacological stimulus is discontinued (Letchworth et al., 2001; Nader et al., 2002). Third, correlations were detected between the cumulative cocaine dose used during the testing interval and cognitive change scores. Moreover, a substantial correlation between the age of cocaine use onset and improvement of working memory in *decreasers* indicates that early age of onset might be a risk factor for sustained cognitive impairment after chronic cocaine use.

Users with escalating cocaine use displayed the largest cognitive decrements in working memory, confirming findings from our larger cross-sectional sample (Vonmoos et al., 2013a) and a meta-analysis (Jovanovski et al., 2005) that this domain is most strongly affected in dependent cocaine users (Vonmoos et al., 2013a). The working memory domain was also improved if cocaine consumption was considerably decreased. These data suggest that either the working memory domain is the most susceptible to cocaine effects, as working memory has previously been associated with monoamine functioning (Robbins and Arnsten, 2009), or working memory tasks are the most reliable and sensitive test parameters. Among controls, the test-retest reliability of the declarative memory (r=.80), GCI (r=.78), and working memory (r=.77) was superior compared with executive function (r=.59) and attention (r=.55).

Overall, the cognitive changes in our longitudinal study appear to be relatively small. However, at baseline, the *increaser* group already had a cumulative lifetime cocaine dose of 1.2kg – a level at

which most cocaine users already display substantial cognitive impairments (Vonmoos et al., 2013a). Given that the *increasers* reported a cumulative cocaine dose of 90g, used between baseline and follow-up, this amount might have been too small to exert stronger cognitive decrements (in addition to a possible ceiling effect).

The reversibility of cognitive impairments in *decreasers*, particularly in working memory and declarative memory, confirms the results of two previous studies indicating verbal (De Oliveira et al., 2009) and immediate (Di Sclafani et al., 2002) memory improvements in cocaine users at 6 months abstinence. However, one study (De Oliveira et al., 2009) had a cross-sectional design, whereas the other (Di Sclafani et al., 2002) postulated improvements but did not apply a test-retest correction. Another study (van Gorp et al., 1999) with cocaine users (n=37) at 45 days of drug abstinence found lasting detrimental effects in nonverbal declarative memory but small improvements in a verbal declarative memory test, similar to the RAVLT results in our study. Moreover, a study with cocaine users (n=30) at 1 month of drug abstinence found no significant differences in learning and delayed recall compared with controls (Bolla et al., 1999). Because dependent cocaine users exhibited reduced activity in frontal regions (Volkow et al., 2009) crucial for cognitive functioning (Cabeza and Nyberg, 2000) and these reductions persisted at least 3 to 4 months after detoxification (Volkow et al., 1992), the abstinence duration in the last two studies mentioned here was supposedly too brief to reveal cognitive recovery effects.

The cognitive recovery process seemed to be particularly pronounced in users who ceased taking cocaine; at follow-up, these users had a GCI score within ±1SD of the control group. However, cocaine users who had been completely abstinent for at least 6 months also reported a relatively low cumulative lifetime dose of cocaine (0.7kg) compared with users with decreased but ongoing cocaine use (5.9kg). Thus, it remains unclear if there is a “point of no return” (i.e., a cumulative cocaine dose beyond which no full recovery can be expected). Nevertheless, we propose that the reversibility of cognitive functions in cocaine users (1) takes some time (at least several months), (2) differs among cognitive domains, (3) depends on the residual level of cocaine use, and (4) is probably related to the amount of lifetime cumulative cocaine dose and age of onset.

This study has some limitations. First, although the group assignment was based on objective hair toxicology covering the last 6 months, for the first six months of the time interval we could rely only on self-reports. Second, the importance of hair melanin pigment for the incorporation of cocaine into the hair structure has not been conclusively clarified (Mieczkowski and Newel, 2000). However, because there is no apparent melanin effect regarding cocaine (Mieczkowski and Kruger, 2007), and 30 of 38 cocaine users in the present study had brownish hair, it is unlikely that the group assignment was affected by this potential constraint. We also used a within-subject design, and, thus, inter-individual differences in hair color play a minor role anyway. Third, our executive function domain

comprised only two parameters because we excluded the IED from follow-up testing. Future longitudinal studies should therefore employ a more comprehensive neuropsychological test battery focusing on executive functioning.

In conclusion, our findings suggest that cognitive performance co-varies with changing cocaine use within a one-year period. Whereas increased cocaine use led to further decrements of cognitive functioning (most strongly pronounced in working memory), decreased cocaine use led to improved cognition, particularly in the memory domains. Remarkably, cocaine users who completely ceased their consumption attained the same cognitive performance level as controls. Previous research has discussed the possibility of neuroenhancement in stimulant users (Sofuoglu, 2010). Our findings suggest that drug abstinence is the best way to enhance cognitive performance in stimulant users. Moreover, abstinence has a more beneficial side-effect profile than any psychopharmacological intervention. Consequently, the use of prescription stimulants to treat cognitive deficits in stimulant users has to be questioned given that methylphenidate and amphetamines likely produce or even prolong neuroplasticity induced by cocaine or other illegal stimulants as they have similar mechanisms of action (Svetlov et al., 2007). Finally, the general reversibility of cognitive deficits also indicates that drug-induced neuroadaptations can probably be remodulated by psychotherapeutical or pharmacological interventions, which might help to achieve and maintain abstinence.

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Conflict of interest disclosures:

All authors declare no conflict of interest. The funders of the study (Swiss National Science Foundation, Olga Mayenfisch Foundation) did not influence the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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4.7 Supplementary material

4.7.1 Methods

sMethods 1: Recruitment and selection

The recruitment focused on the greater area of Zurich and lasted from January 2010 (start recruitment) until March 2013 (finish of the follow-up). Participants were recruited via advertisements in local newspapers, online media, drug prevention and treatment centers, psychiatric hospitals, and by word of mouth. Eight-hundred-and-four prospective participants underwent a standardized telephone interview, whereof 240 subjects were tested in the cross-sectional study. Six participants were not re-invited to participate in the follow-up study (refusal study participation, psychiatric disorders or first-grade family member with schizophrenia). The remaining 234 participants (138 cocaine users, 96 controls) were contacted and invited for a follow-up test session twelve months after baseline testing. One-hundred-and-two participants (59 cocaine users, 43 controls) were not available for the follow-up study due to different reasons (not answering, losing interest, time reasons, death). One-hundred-and-thirty-two participants (56%; 79 cocaine users, 53 controls) agreed to be re-tested and participated in the follow-up. Twenty-seven of these subjects (22 cocaine users, 5 controls) had to be excluded from the final analyses due to hair analyses revealing illegal drug use not allowed by our exclusion criteria (e.g., opioids or excessive MDMA intake) or due to use of psychotropic medication (e.g., antipsychotics or antidepressants).

sMethods 2: Construction of cognitive domain scores

Thirteen predefined main cognitive test parameters were z-transformed on the basis of means and standard deviations of the control group (n=48) at t1. If necessary, test scores were reversed so that high scores always indicated a better cognitive performance. These parameters were reduced to the four cognitive domains attention, working memory, declarative memory, and executive functions according to theoretical a priori considerations and in accordance with previous literature findings as cited below. Furthermore, the four z-scored domains were equally integrated into a broad global cognitive index (GCI). Apart from the non-consideration of two CANTAB Intra/Extradimensional Set Shifting Task (IED) parameters, we used exactly the same approach as in the previously published cross-sectional study (Vonmoos et al., 2013a).

Attention. To assess attention, we primarily focused on sustained attention by including the two RVP parameters discrimination performance A' and total of hits (Jones et al., 1992). In order to diversify this domain, we further added the RAVLT parameter trial 1, a supraspan measure with a strong attentional component (Lezak et al., 2004).

Working memory. The SWM parameter total errors tested the capability to retain spatial information and to manipulate remembered items in the working memory (Morris et al., 1988). The LNST score measured verbal working memory by summing up the number of correct responses (Wechsler, 1997). The PAL first trial memory score measured visual working memory by counting the number of correctly located patterns after the first presentation (Sahakian et al., 1988).

Declarative memory. Three RAVLT parameters were included to assess the verbal declarative memory performance: ∑trials 1-5, delayed recall trial 7, and adjusted recognition performance p(A) (Helmstaedter et al., 2001). Furthermore, the two PAL parameters (adjusted total of errors and adjusted total of trials) were used to capture visual declarative memory (Sahakian et al., 1988).

Executive functions. Because we excluded the CANTAB IED from the longitudinal analysis due to an evident ceiling effect in t1 (Vonmoos et al., 2013a), the executive functions were measured by only two parameters. First, the SWM strategy score assessed the applied heuristic strategies (Morris et al., 1988), a typical feature of the executive functions. Second, the RAVLT recall consistency score is a parameter typically impaired in patients with prefrontal lesions (Benedict et al., 2005; Jokeit et al., 1997) and related with measures of executive functions (Beebe et al., 2000).

4.7.2 Results

sTable 1. Pattern and amount of drug use at baseline

	Controls (n=48)	Cocaine Increasers (n=19)	Cocaine Decreasers (n=19)	Value	df,df_{err}	p
Alcohol						
Grams per week[c]	119.9 (136.8)	169.4 (129.2)	155.3 (146.4)	1.07[a]	2,83	.35
Years of use	13.3 (8.8)	13.7 (7.6)	12 (7.3)	.23[a]	2,83	.79
Nicotine						
Cigarettes per day[c]	8.7 (8.7)	12.8 (11.2)	9.5 (8.2)	1.38[a]	2,83	.26
Years of use	9.3 (8.3)	10.4 (8.9)	12.7 (10.3)	.95[a]	2,83	.39
Cannabis						
Grams per week[c]	0.6 (1.6)	3.3 (8.9)	1.2 (2.3)	2.38[a]	2,83	.10
Years of use	4.5 (4.9)	9.5 (8.5)*	10.1 (9.7)*	5.92[a]	2,83	**.004**
Cumulative dose (grams)	980 (3985)	3199 (5899)	2606 (6359)	1.61[a]	2,83	.21
Last consumption (days)[d]	39.3 (1.6)	10.0 (0.4)	25.4 (1.1)	2.19[a]	2,45	.12
Urine toxicology (neg/pos)[e]	42/6	15/4	14/5	17.60[b]	4	**.001**
Amphetamine						
Grams per week[c]	0.0 (0.1)	0.1 (0.1)**	0.0 (0.1)	5.18[a]	2,83	**.008**
Years of use	0.0 (0.0)	3.3 (4.0)***	1.3 (3.1)°	13 .73[a]	2,83	**<.001**
Cumulative dose (grams)	0.0 (0.1)	56.0 (177.6)*	16.2 (35.9)	2.99[a]	2,83	.06
Last consumption (days)	121.6 (5.1)	73.6 (3.1)	90.9 (3.8)	.29[a]	2,11	.75
Hair analysis AMPH pg/mg[f]	1 (9)	75 (205)*	3 (14)	4.35[a]	2,83	**.02**
MDMA						
Tablets per week[a]	0.0 (0.0)	0.0 (0.1)***	0.0 (0.0)°	7.42 [a]	2,83	**.001**
Years of use	0.3 (1.0)	3.5 (4.5)***	2.4 (4.6)*	8.42[a]	2,83	**<.001**
Cumulative dose (tablets)	1.3 (4.0)	108.8 (249.7)**	18.7 (46.2)	5.71[a]	2,83	**.005**
Last consumption (days)	5 (0.2)	89.9 (3.7)	40.2 (1.7)	1.63[a]	2,9	.25
Hair analysis MDMA pg/mg[f]	7 (30)	251 (678)	413 (1452)	2.23[a]	2,83	.11
GHB						
Cumulative dose (pipettes)	0.0 (0.0)	0.5 (0.7)	0.5 (1.7)	3.36[a]	2,83	**.04**
Hallucinogens						
Cumulative dose (times)	0.9 (2.2)	27.9 (72.8)*	9.9 (22.9)	3.92[a]	2,83	**.02**
Methlyphenidate						
Cumulative dose (tablets)	0.0 (0.0)	20.2 (60.4)*	0.5 (2.3)	3.76[a]	2,83	**.03**
Hair analysis MPH pg/mg[f]	0 (0)	22 (98)	0 (0)	1.80[a]	2,83	.17

Means and standard deviations. Use frequency, duration of use, and cumulative doses are averaged within the total group.
[a] ANOVA (all groups, with significant Sidak post-hoc test vs. control group: *p<.05; **p<.01; ***p<.001; vs. cocaine increaser: °p<.05).
[b] χ^2 test (all groups) for frequency data.
[c] Average use during the last 6 months.
[d] Last consumption is averaged only for persons who used the drug in the last 6 months.
[e] Cut-off values for Tetrahydrocannabinol 50 ng/ml (Substance Abuse and Mental Health Services Administration, 2008).
[f] Cut-off value for amphetamines/MDMA = 200 pg/mg (Society of Hair Testing, 2004).

sTable 2. Pattern and amount of drug use at one-year follow-up

	Controls (n=48)	Cocaine Increasers (n=19)	Cocaine Decreasers (n=19)	Value	df, df_{err}	p
Alcohol						
Grams per week[c]	104.3 (88.6)	259.7 (244.5)***	127.4 (141.4)°	7.71 [a]	2,83	**<.001**
Years of use	14.0 (8.7)	14.8 (7.5)	12.6 (7.9)	.34[a]	2,83	.71
Nicotine						
Cigarettes per day[c]	8.2 (8.7)	13.4 (12.0)	8.2 (7.8)	2.31[a]	2,83	.11
Years of use	10.5 (8.8)	12.5 (8.6)	12.6 (9.9)	.56[a]	2,83	.57
Cannabis						
Grams per week[c]	0.5 (1.6)	2.1 (4.6)	1.1 (2.7)	2.28[a]	2,83	.11
Years of use	4.6 (5.9)	10.5 (9.8)*	8.6 (9.7)	4.64[a]	2,83	**.01**
Cumulative dose (grams)	53.4 (180)	217.8 (526.5)	84.7 (189.6)	2.15[a]	2,83	.12
Last consumption (days)[d]	36.5 (1.5)	9.7 (0.4)	50.8 (2.1)	1.20[a]	2,42	.31
Urine toxicology (neg/pos)[e]	42/6	7/12	15/4	20.36[b]	4	**<.001**
Amphetamine						
Grams per week[c]	0.0 (0.0)	0.1 (0.2)**	0.0 (0.1)	5.89[a]	2,83	**.004**
Years of use	0.1 (0.5)	3.2 (4.9)**	2.7 (5.5)*	7.46[a]	2,83	**.001**
Cumulative dose (grams)	0.0 (0.1)	4.4 (8.9)**	1.4 (3.5)	6.47[a]	2,83	**.002**
Last consumption (days)	17.5 (0.7)	35.7 (1.5)	99.8 (4.2)	1.48[a]	2,10	.27
Hair analysis AMPH pg/mg[f]	0 (0)	77 (153)	53 (229)	2.89[a]	2,83	.06
MDMA						
Tablets per week[a]	0.0 (0.0)	0.4 (0.9)**	0.0 (0.0)°	5.54 [a]	2,83	**.006**
Years of use	0.2 (1.4)	3.8 (5.5)**	3.2 (5.6)*	7.78[a]	2,83	**<.001**
Cumulative dose (tablets)	0.2 (0.8)	17.0 (49.3)*	2.8 (5.2)	3.67[a]	2,83	**.03**
Last consumption (days)	91.2 (3.8)	41.6 (1.7)	47.8 (2.0)	1.11[a]	2,11	.36
Hair analysis MDMA pg/mg[f]	4 (21)	453 (841)***	139 (310)	7.87[a]	2,83	**<.001**
GHB						
Cumulative dose (pipettes)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	-	2,83	-
Hallucinogens						
Cumulative dose (times)	0.0 (0.0)	1.1 (1.6)***	0.6 (1.5)	8.57[a]	2,83	**<.001**
Methlyphenidate						
Cumulative dose (tablets)	0.0 (0.1)	67.7 (239.5)	0.3 (0.6)	2.72[a]	2,83	.07
Hair analysis MPH pg/mg[f]	0 (0)	59 (182)*	0 (0)	3.62[a]	2,83	**.03**

Means and standard deviations. Use frequency, duration of use, and cumulative doses are averaged within the total group.
[a] ANOVA (all groups, with significant Sidak post-hoc test vs. control group: *p<.05; **p<.01; ***p<.001; vs. cocaine increaser: °p<.05).
[b] χ^2 test (all groups) for frequency data.
[c] Average use during the last 6 months.
[d] Last consumption is averaged only for persons who used the drug in the last 6 months.
[e] Cut-off values for Tetrahydrocannabinol 50 ng/ml (Substance Abuse and Mental Health Services Administration, 2008).
[f] Cut-off value for amphetamines/MDMA = 200 pg/mg (Society of Hair Testing, 2004).

sTable 3. Correlations between self reported cocaine use parameters and the hair toxicology parameter $Cocaine_{total}$

	Cocaine Users (n=38)	Cocaine Increasers (n=19)	Cocaine Decreasers (n=19)
Cocaine at t1	$Cocaine_{total}$ at t1	$Cocaine_{total}$ at t1	$Cocaine_{total}$ at t1
Times per week	.18	*.48	-.16
Grams per week	-.04	.12	-.18
Years of use	*.38	.39	.35
Max. dose (grams/day)	*.39	-.06	**.67
Cumulative dose (grams)	**.48	.22	**.62
Cocaine between t1 and t2	$Cocaine_{total}$ at t2	$Cocaine_{total}$ at t2	$Cocaine_{total}$ at t2
Times per week	.14	-.05	.03
Grams per week	.08	-.04	.16
Years of use	.07	.12	.28
Max. dose (grams/day)	.29	.40	.06
Cumulative dose (grams)	.02	-.06	-.01

Pearson's product-moment correlations in cocaine users (n=38). Significant correlations are marked: *p<.05; **p<.01.

sTable 4. Correlations between cognitive change scores and cocaine use parameters during the interval period

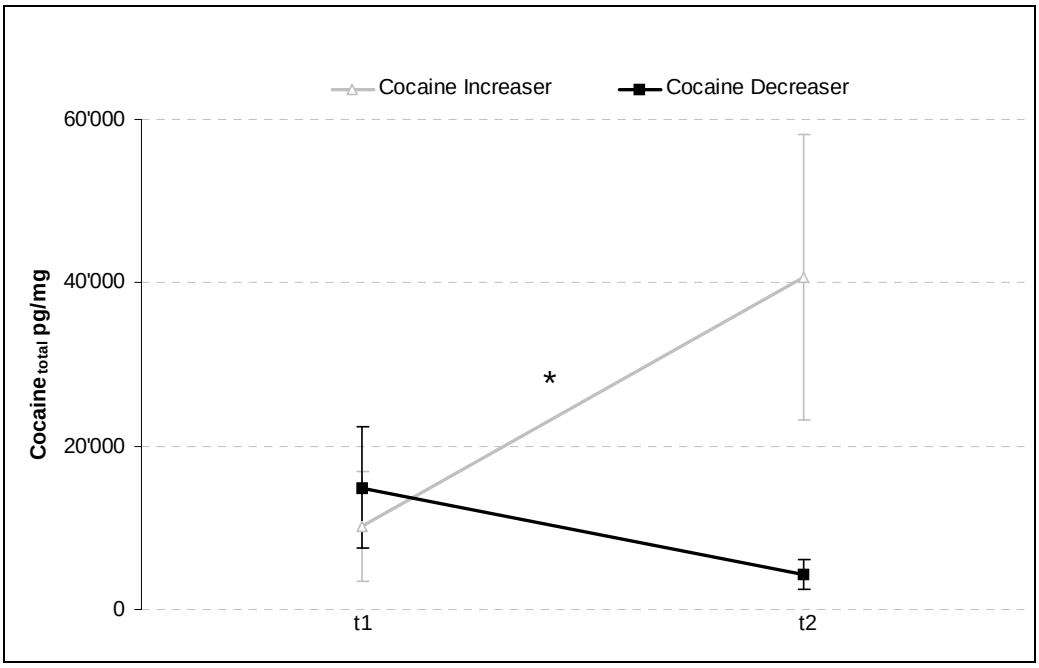
	Cocaine use during the interval period (between t1 and t2)								
Change scores ($\Delta_{t2\text{-}t1}$)	Times per week	Grams per week	Cumulative dose (grams)	Craving for cocaine	Hair analysis Cocaine pg/mg	Hair analysis Benzoylecgonine pg/mg	Hair analysis Cocaethylene pg/mg	Hair analysis Norcocaine pg/mg	Hair analysis $Cocaine_{total}$ pg/mg
Global Cognitive Index			.32						
Neurocognitive domains									
Attention			*.34						
Working memory									
Declarative memory			.30		*-.40	*-.34			*-.39
Executive functions									
Attention									
RVP Discrimination perf. A'			*.36						
RVP Total hits			*.34						
RAVLT Supraspan trial 1									
Working memory									
LNST Score									
SWM Total errors									
PAL First trial memory score								-.30	
Declarative memory									
RAVLT Learning perf. (? trials 1-5)			.31						
RAVLT Adjusted recognition p(A)					*-.41		.30	*.38	*-.39
RAVLT Delayed recall trial 7			**.44			-.32			-.28
PAL Total errors adjusted									
PAL Total trials adjusted									
Executive functions									
SWM Strategy score									
RAVLT Recall consistency in %									

Pearson's product-moment correlations in cocaine users (n=35). Correlations with a p-level below 10% (2-tailed) are shown, while significant correlations are marked: *p<.05; **p<.01.
Three cocaine users with more than 4 SD deviance in cumulative doses or $Cocaine_{total}$ were excluded.

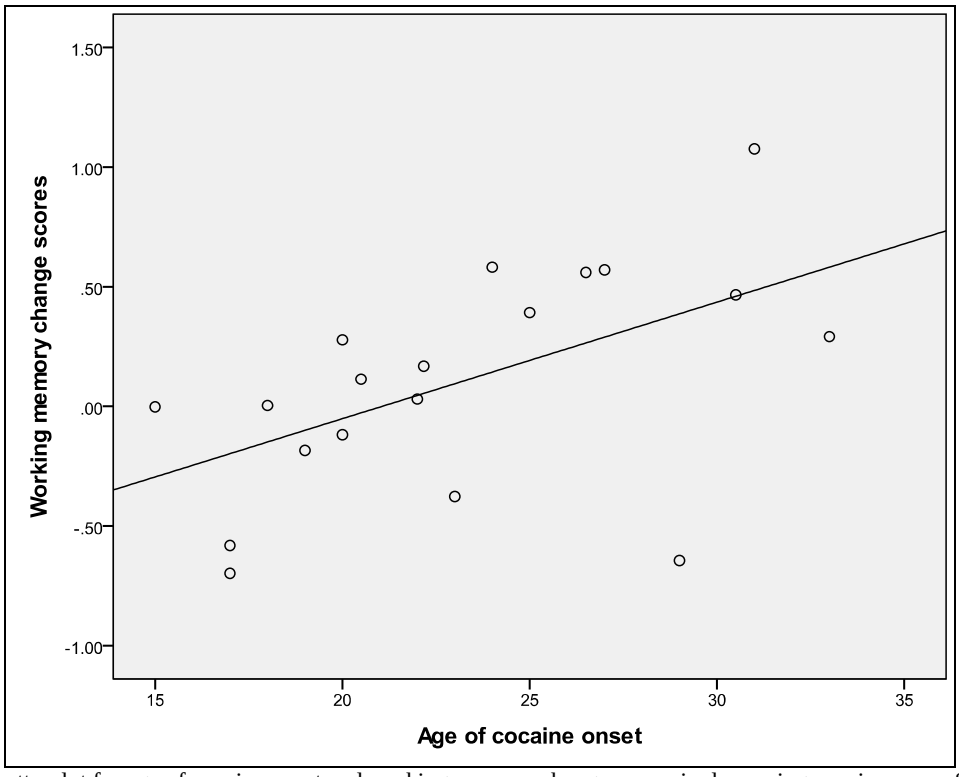
sTable 5. Demographic data and hair analysis in cocaine user subgroups

	Controls (n=48)	Cocaine Increasers low, <10'000 (n=11)	Cocaine Increasers high, >10'000 (n=8)	Cocaine Decreasers ongoing use (n=11)	Cocaine Decreasers no more use (n=8)	F	df, df_{err}	p
Global Cognitive Index ($\Delta_{t2\text{-}t1}$)[d]	0.00 (0.38)	-0.04 (0.48)	-0.15 (0.42)	0.04 (0.51)	0.29 (0.34)	1.3[a]	4,81	.28
Demographic data								
Age, y	30.3 (8.9)	29.5 (8.5)	34.3 (10.4)	33.5 (9.3)	28.5 (6.0)	.80[a]	4,81	.53
Sex (f/m)	16/32	3/8	0/8	3/8	2/6	3.84[b]	4	.43
Verbal IQ (MWT-B)	107.6 (10.0)	104.1 (12.1)	101.3 (5.5)	102.6 (8.5)	105.4 (4.7)	1.28[a]	4,81	.28
Education, y	10.8 (1.8)	10.7 (2.0)	10.0 (1.6)	10.3 (1.8)	9.6 (1.1)	.99[a]	4,81	.42
Smoking (y/n)	37/11	9/2	5/3	8/3	6/2	1.08[b]	4	.90
BDI score (0-63)	3.5 (3.3)	7 (4.5)	7.8 (11.5)	8.5 (7.9)	9.0 (4.6)	3.72[a]	4,81	**.008**
ADHD-SR score (0-22)	7.7 (5.2)	12.5 (9.4)	14.9 (9.8)	13.3 (6.7)	15.1 (7.3)*	4.60[a]	4,81	**.002**
Weeks between t1 and t2	58.2 (10.1)	58.4 (11.0)	60.6 (14.2)	62.4 (13.9)	61.2 (16.4)	.39[a]	4,81	.81
Hair analysis $Cocaine_{total}$ pg/mg								
t1	-	2930 (3014)	20334 (44548)	23842 (40682)	2569 (2630)	1.37[c]	3,34	.27
t2	-	5794 (3395)°°	88664 (101626)	7234 (9858)°°	121 (2 09)°°	6.90 [c]	3,34	**<.001**
$\Delta_{t2\text{-}t1}$	-	+2864 (2395)°	+68331 (83778)	-16608 (34498)°°	-2 447 (2582)°	6.82 [c]	3,34	**.001**

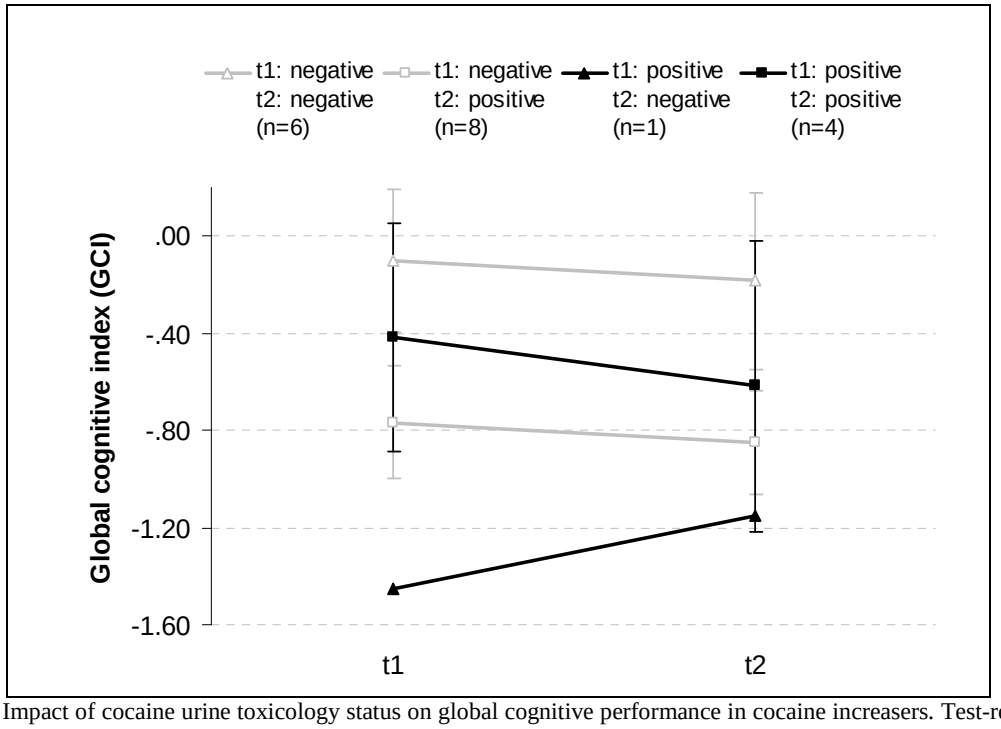
[a] ANOVA (all groups, with significant Sidak post-hoc test vs. control group:*p<.05).
[b] χ^2 test (all groups) for frequency data.
[c] ANOVA (only cocaine user groups, with significant Sidak post-hoc test vs. subgroup cocaine increaser high: °p<.05; °°p<.01; °°°p<.001).
[d] GCI change scores corrected for the test-retest effect.



sFigure 1. Hair concentration $Cocaine_{total}$ in cocaine increasers and decreasers at baseline and follow-up. Hair concentration $Cocaine_{total}$ in cocaine increasers (n=19) and cocaine decreasers (n=19). Means and standard errors. *indicates a significant change (t_{18}=2.14, p<.05) in $Cocaine_{total}$ from t1 to t2.



sFigure 2. Scatterplot for age of cocaine onset and working memory change scores in decreasing cocaine users. Scatterplot for the correlation between age of cocaine onset and test-retest effect corrected working memory change scores ($\Delta_{t2\text{-}t1}$) in decreasing cocaine users (n=19). Pearson's product-moment correlation analyses: r=.54, p=.02.



sFigure 3. Impact of cocaine urine toxicology status on global cognitive performance in cocaine increasers. Test-retest effect corrected mean global cognitive index (GCI) change scores and standard errors in groups stratified for urine toxicology (negative/positive) at baseline and follow-up in cocaine increasers (n=19). Paired Student *t*-tests were non-significant for neg-neg (t_5=-.38, p=.72), neg-pos (t_7=-.55, p=.60), and pos-pos (t_3=-.83, p=.47). Only one cocaine user had a positive urine sample in t1 and a negative urine sample in t2. Therefore, it was not possible to apply the paired Student *t*-test.

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5 General Discussion

The present doctoral thesis aimed to clarify the role of long-term cocaine use with regard to cognitive functioning. The primary goal was to capture selective cocaine-related aspects of cognitive functioning and impulsivity in a cross-sectional design and to further investigate the development of cognitive performance in cocaine users by means of a one-year-longitudinal study with a second test session.

The first study concerned itself with the cognitive performance in relatively pure recreational and dependent cocaine users. The second study examined trait and motor impulsivity in recreational and dependent cocaine users. The third study intended to determine the relation between a changing pattern of cocaine use and changes of cognitive functioning. This final chapter now aims to briefly summarize the three papers' findings, strengths, and limitations. Subsequently, concrete implications for daily life, prevention, treatment, and future research shall be discussed.

5.1 Cognitive performance in recreational and dependent cocaine users

The results of the first study confirmed previous findings indicating that dependent cocaine use is associated with broad cognitive impairments in the domains attention, working memory, declarative memory, and parts of the executive functions (Jovanovski et al., 2005; Woicik et al., 2009). However, in all four domains, recreational cocaine users performed intermediately between controls and dependent users and displayed significant deficits, foremost in the domains attention and working memory. Notably, the same two domains were the most strongly affected in an earlier meta-analysis (Jovanovski et al., 2005). Furthermore, this finding is in line with previous studies from the ZuCo^{2}St indicating catecholamine dysfunction already at a recreational level of use (Hulka et al., 2013b; Preller et al., 2013b). In sum and as already demonstrated in studies with smaller samples (Colzato et al., 2009a; Rahman and Clarke, 2005; Soar et al., 2012), cognitive deficits occur already at a recreational and non-dependent level of cocaine use. Additional correlation and regression analyses revealed negative associations between cognitive performance and cocaine metabolites in the hair, cumulative cocaine dose, and duration of cocaine use. Although investigated in a cross-sectional design, these results suggest – in accordance with some other cross-sectional studies (Beveridge et al., 2008; Ersche et al., 2011; Woicik et al., 2009) - that cognitive impairments might be at least partially cocaine-induced. Moreover, we found for the first time that symptoms of the attention deficit hyperactivity disorder (ADHD) and depression as well as craving for cocaine and early age of onset are important modulators of cognitive functioning in cocaine users. Because ADHD is characterized by a diminished performance in attention and inhibition (Valera et al., 2010) and – similarly as is cocaine users (Volkow et al., 2009; Volkow et al., 2004) - associated with abnormalities in the prefrontal cortex and catecholamine systems (Liston et al., 2011; Shen et al., 2012), a mutual aggravation of detrimental effects on cognitive performance might be assumed. By contrast and in opposite to an earlier study

(Woicik et al., 2009), recent cocaine use as measured by positive urine toxicology seemed to be less important. However, cognitive dysfunction is even present in cocaine users without craving, depression, or ADHD symptoms. Last but not least, we were firstly able to demonstrate that the risk for cognitive impairment increases with ascending cumulative cocaine doses - in particular, if estimated lifetime doses of 500g to 1000g cocaine are exceeded. The according neuropsychological profile suggests prefrontal dysfunction as the common denominator of these cognitive impairments (Cabeza and Nyberg, 2000), which is in line with previous findings showing alterations of the frontostriatal dopamine system in addicted cocaine users (Bolla et al., 2004; Ersche et al., 2012a; Ersche et al., 2012b). In sum, these results indicate gradual impairments in both, recreational and dependent cocaine users, while clinically relevant cognitive deficits seem to arise with long-term cocaine use as best reflected by cumulative cocaine dose.

5.2 Impulsivity in recreational and dependent cocaine users

The second study confirmed previous findings of elevated trait impulsivity and novelty seeking scores in cocaine users compared with controls (Ersche et al., 2011; Ersche et al., 2010; Moeller et al., 2002). Because both, recreational and dependent cocaine users, displayed increased trait impulsivity, it can be excluded that this is an exclusive feature of addiction. Furthermore, trait impulsivity was strongly associated with an increased number of ADHD and depression symptoms and correlated significantly with the two long-term cocaine intake parameters cumulative cocaine dose and duration of use. The detection and determination of ADHD and depression as important factors for trait impulsivity in cocaine users is in line with the frequent comorbidity of both disorders with drug addiction (Swendsen and Merikangas, 2000; van Emmerik-van Oortmerssen et al., 2012). In addition, both disorders, ADHD and depression, share some fundamental features with the impulsivity concept; Whereas ADHD is characterized by inattentive and impulsive behavior (Wilson, 2007), depression and trait impulsivity are closely related in alcohol-dependent patients (Jakubczyk et al., 2012), and hopelessness and impulsivity are strongly associated in subjects with bipolar disorder (Swann et al., 2008).

By contrast, none of the behavioral motor impulsivity measures showed significant group effects or correlated with any of the cocaine use parameters. Thus, we confirmed previous findings showing that the applied impulsivity-related CANTAB RVP parameters might not suitable to detect potential impulsive behavior in cocaine users (Ersche et al., 2011; Soar et al., 2012). Moreover, we demonstrated that an impulsivity measurement by the Stop-Signal task is a delicate procedure and that small changes in the study design and the application of the Stop-Signal task might have a fundamental impact on the study's outcome. Therefore, our results cannot definitely determine if there is indeed a dissociation between trait impulsivity and behavioral impulsivity or whether these

differences just highlight difficulties in the operationalization and measurement of facets of behavioral impulsivity. Finally, in accordance with previous literature, correlations among the self-reported impulsivity measures were high, but these measures correlated only scarcely with behavioral impulsivity task parameters (Ersche et al., 2011; Lijffijt et al., 2004; Reynolds et al., 2006). Therefore, our results support the lasting assumption of impulsivity as a multidimensional construct that integrates different aspects and concepts of impulsivity (Evenden, 1999; Perry and Carroll, 2008).

5.3 Cognitive development in increasing and decreasing cocaine users

The third paper extends findings from the first paper and was the first to investigate the relation between objectively changing intensity of cocaine use and development of cognitive functioning. Participants were tested twice at a one-year interval and the intensity of cocaine use was objectively determined by quantitative 6-month hair toxicology analyses. As expected from previous animal studies (Gould et al., 2012; Liu et al., 2008; Porter et al., 2011) and strong dose-effect correlations between several cocaine use parameters and cognitive impairments among cocaine users in the first paper, a substantially increased cocaine use within one year led to deteriorated cognitive performance, foremost in the working memory. By contrast and as expected from preliminary studies with up to 6 months abstinent cocaine users (De Oliveira et al., 2009; Di Sclafani et al., 2002; van Gorp et al., 1999), decreased cocaine use generally improved cognition and showed the strongest enhancement in working and declarative memory. These data suggest that either the working memory is the most susceptible to cocaine effects or working memory tasks are the most reliable and sensitive test parameters. Whereas the first hypothesis is supported by the fact that working memory has previously been associated with monoamine functioning (Robbins and Arnsten, 2009) and a particularly strong association of cognitive remediation therapy with durable working memory improvements in schizophrenia patients (Wykes et al., 2007b), the second hypothesis is supported by a substantially superior test-retest reliability of the declarative (r=.80) and working memory domains (r=.77) compared with the domains of attention (r=.55) and executive function (r=.59). Notably, users who ceased using cocaine seemed to recover completely and attained a similar cognitive performance level as the control group. However, this group was rather small (n=8) and reported a cumulative cocaine lifetime dose of 0.7kg. On the one hand, this amount is substantially smaller than in the users with decreased but ongoing cocaine use (5.9kg) - and therefore the direct group comparison has to be done with caution – on the other hand it still equals a substantial lifetime dose of approximately 7000 lines (Müller et al., 2004), an amount that – in the first paper - has shown to clearly increase the risk for cognitive impairment. Because the general risk for cognitive impairment increases with an early age of cocaine use, the recovery process most likely also depends on the age of cocaine onset. Accordingly, it

remains unclear if there is a “point of no return” and we cannot determine a cumulative cocaine dose beyond which no full recovery can be expected.

In sum, these longitudinal data suggest that cognitive impairment might be partially cocaine-induced but also reversible within one year. This reversibility indicates that neuroplastic adaptations underlie cognitive changes in cocaine users that can potentially be modified in intervention. Finally, these results imply that abstinence might be the best way to enhance cognitive performance in stimulant users.

5.4 Strengths

The design of the ZuCO^{2}St and accordingly the three presented studies feature a number of strengths worth mentioning.

First, the combined application of urine and hair toxicologies allowed a precise and objective drug use characterization over the past six months. Today, urine toxicology analyses are a common feature in drug research and very accurate in detecting recent cocaine ingestion (Moeller et al., 2008). As urine toxicology analyses in our studies were performed by immunoassays, which are only presumptive and potentially biased by external factors (Moeller et al., 2008), positive urine tests did not necessarily indicate a violation of the requested three day cocaine retention period. Accordingly, participants who tested positive for cocaine were not excluded, but the post-acute effects of the drug were investigated. However, in urine samples, cocaine is detectable for maximally five days (Arbeitsgruppe Suchtstoffanalytik, 2006). Therefore, hair toxicology analyses are a reasonable complement in order to extend the continuous drug verification period up to some months. Given that studies investigating drug use are subject to ethical and methodological constraints (Curran, 2000), such objective measurement tools are considered inevitable requirements. Notably, our data confirmed this apprehension, as approximately 20% of the participants in the cross-sectional (46 out of 240 participants) and the longitudinal study (27 out of 132 participants) had to be excluded because their hair toxicology analyses did not match their self-reported drug use declaration and revealed either polytoxic or lack of drug use (e.g., opioids, MDMA).

Second, we excluded participants with severe psychiatric diagnoses (schizophrenia, obsessive-cumpulsive disorder, eating disorder, etc.) or a family history of such severe psychiatric disorders from the study. Nonetheless, some comorbidities such as ADHD or a depressive affinity are frequently associated with cocaine use (Gotlib and Joormann, 2010; Perez de Los Cobos et al., 2011; Swendsen and Merikangas, 2000). Therefore, we systematically analyzed the impact of these variables with correlation, regression, and subgroup analyses.

Third, although the above-mentioned constraints considerably reduced the sample size, the final cross-sectional sample consisted of 194 eligible subjects and was comparatively large for addiction research.

For the longitudinal study, this sample was further diminished, but with 105 eligible subjects still comparatively numerous.

Fourth, including a group of recreational cocaine users in the two cross-sectional design papers was an additional benefit implicating some considerable advantages: Recreational users are supposed to account for a large part of the cocaine users (European Monitoring Centre for Drugs and Drug Addiction, 2012). Accordingly, potential findings have a broad validity. Moreover, because recreational cocaine use can be considered as an intermediate step towards addiction, the separate analysis of non-dependent users allowed a clear distinction between aspects specifically related to addiction and aspects presumably related to recreational stimulant use. Furthermore, the investigation of recreational cocaine users had the advantage of substantially less comorbidities and polytoxic drug use, as these features are often specifically related to drug addiction.

Fifth, to date it is still unsettled whether cognitive impairments are preexistent, cocaine-induced, or both. However, by means of our investigations, we were able to further clarify this relationship. In the first study, cognitive performance correlated negatively with long-term cocaine use parameters such as cumulative dose and duration of use. Moreover, the risk for cognitive impairments was clearly associated with an increased cumulative use of cocaine. In the third study, the cocaine use pattern during the one-year interval period was linked to developments in cognitive performance. In sum, these results clearly indicate an at least partially cocaine-induced variability in cognitive performance. However, this conclusion cannot exclude that (a) other factors beside cocaine have a decisive impact on cognitive functioning and (b) that there are some (additional) preexistent cognitive vulnerabilities in cocaine users.

5.5 Limitations

Notwithstanding the outlined strengths of the ZuCo^{2}St, there are also some inevitable limitations: The major advantage of all three studies, the applied hair toxicology analyses, was only analyzed for the last six months prior to the test session. Notably, for the time before that, the drug use history was based exclusively on self-reports. However, because values from hair toxicology analyses and self-reports were compared and verified by trained psychologists, a presumably substantial part of the intentionally inadequate self-reports was detected and eliminated.

Another limitation is the fact that cocaine dependence was solely diagnosed according to the DSM-IV criteria. Although the Structured Clinical Interview for DSM-IV Axis I (SCID-I) disorders was carried out by trained psychologists, it is nonetheless a manipulable instrument as it depends solely on self-perception but does not consider important drug use features such as duration and amount of cumulative dose. Thus, with regard to the mentioned often inaccurate self-reports, some subjects in the recreational cocaine user group might be misclassified as non-dependent.

Regarding the applied measurement tools, the three studies featured some test-implicit weaknesses. Although an extensive neuropsychological test battery has been employed in the first and third study, the measurement of the executive function domain was rather rudimentary. On the one hand, the executive functions are considered a heterogeneous concept including different high-level functions (Miyake et al., 2000). Therefore, it is very complex and costly to completely operationalize the whole concept. On the other hand, the CANTAB Intra/Extradimensional Set Shifting Task applied in the cross-sectional study revealed an evident ceiling effect and was consequently excluded from the longitudinal analysis. Hence, our executive function domain did probably not cover the broad variety of executive functions. In the second study, none of the behavioral motor impulsivity measures showed a substantial linkage with any cocaine use parameter. Thus, it remains unclear whether there is indeed no mentionable relation or if this result rather highlights difficulties in the operationalization and measurement of motor impulsivity.

5.6 Implications

The original aim for this behavioral research in cocaine users is to extend the knowledge on the linkage between cocaine use and cognitive processes. Particularly because there is still no effective pharmacological treatment for cocaine addiction (Sofuoglu, 2010), a better understanding is needed to develop new therapeutic instruments (Gould, 2010). Although the three presented studies do not include a final or ready-to-use intervention approach, they nonetheless provide some helpful insights and implications with regard to the development of concrete prevention and intervention processes.

First, results from the first and third study supplemented by findings from two other ZuCo^2-studies (Hulka et al., 2013b; Preller et al., 2013b) suggest alterations of catecholamine neurotransmission already in recreational cocaine users and escalating with ongoing cocaine use. These dopaminergic disruptions are linked to craving and loss of control, generally leading to compulsive drug administration in cocaine addiction (Volkow et al., 1997). Hence, this process suggests informational and educational needs to prevent it from turning into an autonomous vicious circle (Sofuoglu, 2010).

Second, both studies on cognitive functioning indicated a linkage between an early age of cocaine onset and an increasing risk for cognitive impairment. Because the developing brain is particularly susceptible to the effects of drugs (Gould, 2010), this finding implicates the necessity for an education and prevention as early as possible.

Third, having a mental illness clearly increases the risk for substance use (Kavanagh et al., 2004; Kessler et al., 1997; Pettinati et al., 2013), primarily because the use of drugs is presumed to relief depression, anxiety, and boredom or to facilitate relaxing and socializing processes (Cleary et al., 2009). Unfortunately, the adverse impact on cognition may be dangerous and harmful, particularly in combination with cognitive problems related to these mental disorders (Gould, 2010). Accordingly,

research and intervention have to consider and integrate both, mental health and substance use issues (Drake et al., 2008). With regard to cocaine, the first study found that symptoms of ADHD and depression as well as craving for cocaine were important modulators of cognitive functioning, while the second study revealed that trait impulsivity was strongly associated with an increased number of ADHD and depression symptoms. Additionally, another ZuCo^2-study reported enhanced craving symptoms for cocaine users with an ADHD diagnosis (Preller et al., 2013b). In sum, these findings suggest that affective disorders and especially ADHD are a substantial additional burden for cocaine users (Robbins and Arnsten, 2009; Teichner et al., 2001): (a) because cocaine use is associated with altered catecholamine signaling (Volkow et al., 2009; Volkow et al., 2004) – in particular if ADHD or craving symptoms are present (Preller et al., 2013b) – cocaine users with an affective disorder or ADHD are at greater risk for the previously described transition from recreational to dependent use and (b) because further important symptoms and factors have to be considered in treatment.

Fourth, impulsivity has been recognized as a fundamental feature of substance use (de Wit, 2009). Converging evidence from studies in drug-addicted populations suggest an association between addiction and neuroadaptive changes in the frontostriatal network (Ersche et al., 2011; Goldstein and Volkow, 2011; Sofuoglu, 2010). Because the ventromedial prefrontal cortex and the dorsal anterior cingulate cortex are closely linked to cognitive functions such as decision-making and inhibitory control (Yucel and Lubman, 2007), and the orbitofrontal cortex is associated with compulsivity (Ersche et al., 2011), these changes are likely to influence impulsive and compulsive behavior with regard to drug use (Ersche et al., 2011; Sofuoglu, 2010). Furthermore, impairments in these functions are often compounded by other factors, such as early age of onset, polydrug use, and mental illness (Yucel and Lubman, 2007). In sum, these findings suggest for cocaine users an increased risk for impulsive decisions and a lack of inhibitory and therefore also cognitive control. Consequently, previous literature consistently reported impaired cognitive control in cocaine users (Beveridge et al., 2008; Bolla et al., 2004; Garavan and Hester, 2007) that results in a particular vulnerability to make the transition from recreational to compulsive and accordingly to dependent cocaine use (Ersche et al., 2011). Treatment approaches need to consider such neuroplastic adaptions and implications and incorporate relevant compensatory strategies into treatment (Yucel and Lubman, 2007) with the goal to circumvent compulsive habits (Ryan, 2006).

Fifth, possible cognitive deficits should be considered in treatment planning. In recent years, mounting evidence linked cognitive impairments to poor treatment outcome in stimulant users (Sofuoglu, 2010). Particularly, research suggested that cognitive impairments and impulsivity as measured by the BIS-11 decrease treatment retention and increase treatment dropouts in cocaine dependent patients (Aharonovich et al., 2006; Aharonovich et al., 2003; Moeller et al., 2001b; Teichner et al., 2002). Furthermore, Streeter et al. (2008) discovered a close and reliable linkage between cognitive functioning as measured by the Stroop task and treatment attrition. Particularly in prevention, when people do not necessarily have the ability or time to take in new or even contradictive information, the

main messages have to be short, understandable, and easy to remember. By contrast, in ongoing treatments the information may be a bit more comprehensive. However, it is extremely important in both cases that the main messages are not excessively demanding in order not to overtax the target subjects. Otherwise, cognitive deficits may hinder the persons' ability to benefit from counseling and extend the treatment or the time to incorporate abstinence-sustaining strategies into their daily routines (Gould, 2010).

Consequently, another treatment possibility would be to enhance the patients' cognitive abilities as for example cognitive remediation therapies have shown to be beneficial in treatment of other – partly closely related – psychiatric disorders such as schizophrenia (Wykes et al., 2007a; Wykes et al., 2007b), depression (Elgamal et al., 2007), anorexia nervosa (Tchanturia et al., 2007; Whitney et al., 2008), and ADHD (O'Connell et al., 2006; Stevenson et al., 2002). With specific regard to cocaine users, it was already shown that neurocognitive training on working memory decreases the capability of delay discounting (Bickel et al., 2011), a fundamental feature of cognitive functioning. Likewise, another study reported that performance on cognitive flexibility and inhibition tasks is related to more adaptive cognitive styles and inversely related to some components of learned helplessness, whereas working memory performance is related to a more global failure attribution (García et al., 2005).

Sixth, the third study indicates the reversibility of cognitive effects in decreasing cocaine users and even more pronounced in users who ceased using cocaine. Because this conclusion was drawn from a small sample that made it impossible to adequately investigate all probable co-factors, this postulated reversibility is by no means a carte blanche for unreserved cocaine use. However, the data indicate that even long-term cocaine use does not necessarily lead to irreversible cognitive deficits, a finding with enormous impact for the motivation to cease cocaine use or to remain abstinent.

Altogether, these findings suggest that the best way to tackle cocaine addiction is prevention by means of an early and simple education that aims to suppress the motivational impact of drug cues. Furthermore, support and treatment seem to be more promising and effective in an early, non-dependent stage of use. However, our data also suggest that users who ceased using cocaine seem to recover from cognitive impairment, indicating that it is never too late to stop using cocaine. However, more research is needed to doubtlessly accept this finding. Furthermore, there is currently only rudimentary knowledge on co-factors easing or hindering this development. And last but no least, it should not be forgotten that also among cocaine users cognitive impacts differ, depending on variations in environmental factors and genetics (Gould, 2010).

5.7 Perspective

Overall, the three studies presented in chapter 2 to 4 contributed to filling some fundamental research gaps by further characterizing recreational cocaine users and enhancing the current knowledge with

regard to consequences of changing cocaine use patterns and causality. However, there are still some open questions and weaknesses that should be addressed in future research.

A fundamental problem in the comparability of studies investigating the consequences of cocaine use is the inconsistency of study samples and designs. Substantial differences regarding potentially important co-factors such as polytoxic drug use, mental illness, verification of self-reports, recent cocaine use, route of administration, measurement methods, concept definitions, and diluents in the drug complicate a systematic and coherent research. Accordingly, small determinants, sometimes not even disclosed in the research manuscripts, may have a fundamental impact on results and findings. For example, to investigate the impact of recent drug use on a certain dependent variable, the concept of "recent drug use" (1) must be regarded as essential, (2) needs to be defined (does recent mean 48h or 72h), (3) has to be operationalized (subjective self-report or objective urine toxicology), and (4) must be systematically analyzed. In all of these steps different interpretations and solutions are correct, but might result in completely different findings. Therefore, the objectification of drug use parameters resulting in standardized and comparable values seems to be an essential feature of future drug research. However, with regard to some co-factors, such as for example polytoxic drug use, a complete standardization of study samples seems impossible.

Now that – in previous as well as in the three presented studies – a robust cognitive profile of cocaine users has been discovered, the next challenge is doubtlessly to clarify the exact pattern and interaction of neurocognitive effects and its causal relation with addiction (Garavan and Hester, 2007). In this sense, further longitudinal studies and - even more important - prospective studies should be conducted to fully answer the question of causality between the use of cocaine and cognitive functioning.

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